QUALIFIED HEALTH CLAIM PETITION

100% WHEY PROTEIN PARTIALLY HYDROLYZED in Infant Formula and REDUCING THE RISK OF ALLERGY IN INFANTS

SUMMARY OF SCIENTIFIC DATA

SECTION CONTENTS **Page**

DEFINITION OF TERMS

In order to ensure that this petition relied on a generally agreed upon definition of the disease condition in question, Nestlé canvassed several available sources for a definition of "allergy". No definition of allergy was found on the websites for FDA, CDC or NIH, per se. However, the CDC site had a link to the American Academy of Allergy Asthma and Immunology website, which defines allergy as a"harmful, increased susceptibility to a specific substance" also known as "hypersensitivity" (AAAAI 2005). Similarly, the NIH website links to the "Medline Plus" on-line encyclopedia, which defines allergy as "an exaggerated immune response or reaction to substances that are generally not harmful" (Medline Plus 2005). To find a definition more specific to infants and to foods, the Company checked the Pediatric Nutrition Handbook published by the American Academy of Pediatrics (AAP 2004)), which defines "Food hypersensitivity (allergy) as "classic allergy hypersensitivity reaction to food or food additives involving IgE antibody and release of chemical mediators."

Having gathered this assurance that this key definition was consistent across multiple sources, Nestlé provides the following glossary (based on definitions by the World Allergy Organization Project Report and Guidelines, 2004) as an easy reference for the terms used in this petition:

Allergy: Allergy is a hypersensitivity reaction initiated by immunological mechanisms.

Allergens: Allergens are antigens which cause allergy.

Atopy: Atopy is a personal and/or familial tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposure to allergens, usually proteins.

Dermatitis: The umbrella term for a local inflammation of the skin should be dermatitis. Eczema is not one, single disease but rather an aggregation of several diseases with certain characteristics in common. The subgroup related to allergic asthma and rhinoconjunctivitis (i.e., eczema in a person of atopic constitution) should be called atopic eczema [referred to herein as "atopic dermatitis" or "AD"].

Primary Prevention: Prevention of immunological sensitization (i.e., the development of IgE antibodies).

THE SUBSTANCE/DISEASE RELATIONSHIP

Overview

Primary prevention, where the risk of immunologic sensitization is reduced, would be the ideal approach to reducing the risk of allergy in infants. At the present time, the best means to prevent food allergy is food allergen avoidance. In infancy, this is generally achieved through the exclusive feeding of breast milk or extensively hydrolyzed infant formulas. Breastfeeding is clearly the best way to feed an infant, but not all infants are breastfed. Extensively hydrolyzed formulas, while widely acknowledged by the medical community for their ability to prevent (as well as treat) allergic symptoms, are specialty formulas not widely accepted for use in healthy infants due to their expense and relatively bitter taste. In order to better address the increasing incidence of allergy in the general population, the distinct and valuable role that 100% Whey-Protein Partially Hydrolyzed infant formula (PHF-W) can play in the reduction of risk of allergy in infants should also be acknowledged. The relationship between PHF-W and reducing the risk of infant allergy is best explained in terms of the way it meets the criteria for food allergy prevention strategies set forth by Zeiger 2003. Zeiger focuses on the ability of a given strategy to:

1) *predict the high-risk infant and child*
2) *demonstrate effectiveness of the intervention strategy*
3) *use acceptable interventions*
4) *minimize adverse effects*
5) *generate cost-effective outcomes*

Predictors and Prevention of Allergic Disease: "At-Risk" Populations and the General Population

With respect to Zeiger's 1st criterion, many infants in the general population are, in fact, at risk of developing allergy but are not "predicted" to be at risk, due to the lack of effective and practical means with adequate sensitivity and specificity to predict the "high-risk" infant at birth. Nevertheless, for practical and ethical reasons, the majority of clinical trials investigating PHF-W as a means of primary prevention of allergy have been conducted in infants with a family history of allergy, rather than the general population, since having a family history of allergy increases an infant's risk of developing allergy later in life. While these infants may be referred to as "high risk" or "at risk" by researchers, it is important to note that only healthy infants with no manifestations of allergic disease meet the inclusion criteria for primary prevention studies.

For many chronic diseases, including allergy, a positive family history of a specific disease is a useful marker of risk for developing that particular disease. Besides family history, specific immunologic markers in the blood can be used to identify at-risk infants, but these markers also lack sensitivity and specificity (Wahn 2001) and are not practical for screening purposes at the level of the general population.

Unfortunately, family history is a poor method to rely upon to assess the risk for an individual infant, or to identify most infants in the general population who are at risk. Studies show that comparable absolute numbers of infants with *no* family history of allergy will develop allergy as those who have a family history (Bergmann 1998, Exl 2001, Halken 2000, Bousquet 1986, Kjellman 1977). Thus, approximately 50% of infants who go on to develop atopic disease, and who are therefore "at risk" of developing allergy, <u>do not have</u> a family history of allergy.

Moreover, for all those infants who do have a family history, and could be categorized as being "at risk" by this criterion, there is currently no standardized, validated or practical questionnaire or screening mechanism to obtain this history prior to exposing these infants to intact cow's milk protein. Collection and interpretation of family medical history is rarely applied for the purposes of individual risk-based intervention (Yoon 2002). Adequate medical history is rarely obtained in general practice (Acheson 2000). Currently there is no compulsory or mandated mechanism to obtain family history of allergy in the general population. And, more importantly, no practical screening tool or questionnaire has been developed and sufficiently validated for obtaining an adequate history of allergy in the family.

Consequently, the vast majority of infants actually at risk of developing allergy (whether or not they have a family history) go unidentified until they exhibit signs or symptoms of atopy. Recommendations for allergy prevention focusing on "infants at risk" defined by family history are, therefore, inadequate and ineffective for primary prevention. Until better methods for defining risk are available, interventions are needed which target the broadest possible segment of the population.

The protective effect of PHF-W found in infants with a family history certainly applies to those infants who currently go unidentified (for the reasons mentioned above) despite having such a history. For those infants at risk of developing allergy but who do not have a family history, there is no clear rationale to suggest they would not benefit from similar intervention. In fact, those few trials that have been done investigating the use of PHF-W as a primary prevention strategy for allergy in the general population have produced results similar to those in studies within populations defined as "at risk" by family history (Exl 2000, Exl 1998, Iikura 1995).

As a result, a food allergy prevention strategy for PHF-W logically applies not only to healthy infants who *are* identified as "high risk" by virtue of family history, but also to healthy infants with a family history who *are not* identified in standard clinical practice, as well as to those who have *no family history* of allergy at all – but who are, in fact, at risk – i.e., to the general population of healthy infants.

Demonstrating the Effectiveness of the Intervention Strategy

With respect to the 2nd criterion above, the sound body of literature discussed in more detail later in this section reveals that PHF-W can significantly reduce the risk of allergy in comparison to standard, intact cow's milk infant formulas (CMF). PHF-W are marketed by Nestlé S.A. worldwide. For more than 15 years these formulas have been the subject of multiple clinical trials in various countries throughout the world. While these studies have differed in terms of design and outcomes studied, the results have been consistent in demonstrating that when PHF-W are used as a supplement or replacement for human breast milk, there is a reduction in the incidence of allergy compared to that seen with CMF.

In Section D: Analytical Data – Substance Characterization, Nestlé discusses the global formulation and release criteria by which the Company defines the substance that has been the subject of the series of clinical trials that began in the 1980s and are described in this petition. At present, only one manufacturer offers such a formula in the United States. However, based on the growing body of data demonstrating the special benefit of such a formula, as well as the hoped-for FDA-acknowledgement of the propriety of a qualified health claim regarding this benefit, it can be expected that other infant formula manufacturers will be encouraged to offer similar formulas. It is important to note, however, should other manufacturers seek to use a similar claim, that a careful evaluation of the attributes of both the

protein hydrolysate and the formula matrix must be conducted – and even clinical testing may be necessary – in order to confirm the efficacy of a given formulation.

The value of clinical confirmation was particularly well illustrated in the recent "GINI" study (Von Berg 2003) in which one of the formulas studied was a 100% whey formula *more* hydrolyzed than the PHF-W that is the subject of this petition. The formula was referred to as an "extensively hydrolyzed whey formula" (EHF-W). It is generally assumed that the more hydrolyzed a protein is, the less antigenic it may be. However, the PHF-W formulation was effective in reducing the risk of common symptoms of food allergy (specifically atopic dermatitis) in that study, while the EHF-W was not. This result suggests that not only the specific formulation but also the specific processing may create important distinctions in the ability of hydrolyzed protein in an infant formula to prevent allergy.

Acceptability and Absence of Adverse Effects

In the context of the 3rd criterion above, PHF-W formulas are clearly an "acceptable intervention" for the general population. As routine infant formulas, the nutrient profiles of PHF-W must be consistent with the strict minima and maxima required by the Infant Formula Act (IFA). Moreover, clinical growth studies, thoroughly reviewed by FDA's Office of Nutritional Product, Labeling and Dietary Supplements, in addition to a long history of use in this country and others, have shown that PHF-W are routine infant formulas that support normal growth in infants, comparable to that seen on standard intact cow's milk formulas.

PHF-W from Nestlé has been studied in at least 28 published controlled trials in healthy infants, in which a total of nearly 2300 healthy infants safely received PHF-W, either exclusively or in varying combinations with breastfeeding, for periods of time ranging from 4 weeks to 6 months, with no reports of inadequate growth or other adverse events associated to

the formula. For the more than 675 of these infants who were enrolled in trials documenting growth as a specific outcome, adequate growth was documented in all.[1]

In addition, PHW formula has been commercially available for nearly 20 years worldwide, with no reports of inadequate growth. In the U.S., where it has been commercially available for 15 years, it can be estimated based on volume sold, that over half a million infants per year are raised on PHF-W, either exclusively or as a supplement to breast milk. Nestlé is currently the exclusive provider of infant formula (predominantly PHF-W) for seven state programs under the auspices of the USDA's Women Infants and Children (WIC) supplemental feeding program, a federal nutrition program which feeds approximately half of all U.S. infants.

That PHF-W formulas do not cause adverse health effects, consistent with the 4th criterion above, is demonstrated not only by the clinical growth studies mentioned above, but also by the fact that – as required under the IFA for all U.S. infant formulas – complaint surveillance records must be meticulously investigated by the Company and are regularly reviewed by the FDA. No tendency toward adverse effects due to Nestlé's PHF-W formulas has ever been noted in these investigations or reviews.

Generating Cost-Effective Outcomes

With respect to the 5th criterion above, the capacity to generate cost effective outcomes, PHF-W formulas cannot, of course, compete with breastfeeding. They are, however, certainly a more economical approach for use in the general population than extensively hydrolyzed formulas. Moreover, for infants who are not breast-fed, there is no additional cost at all inherent in choosing PHF-W over other brand-name routine formulas.

[1] These "safety" studies were not included in this petition unless they also had incidence of allergy as an outcome. However, if the agency is interested in reviewing this material, Nestlé would be happy to provide additional information.

So, while the potential societal savings in healthcare costs from reducing the incidence of allergy are already significant, they take on added significance in light of the fact that these savings would come at absolutely no societal cost.

As discussed in the Preliminary Requirements section, allergy – particularly as atopic dermatitis – is a major public health problem. Allergic disease begins in infancy and can impact not only the health of the individual infant, but also the quality of life and economics of the whole family. Given the cost impact on quality of life and inconvenience of treatment, and the possibility the atopic march may lead to even more serious concerns later in life, the ideal solution is primary prevention (see Appendix C-I for an analysis of economic implications by Chandra 1997 and Zeiger 1998). Breastfeeding is by far the best method of feeding an infant, under virtually any circumstances. For infants who are not exclusively breastfed, and who are *identified* as being at risk of developing allergy, an extensively hydrolyzed formula might be recommended – and, for such an infant, the expense and lack of palatability of may be tolerable. But, given the number of "at risk" infants who will *never be identified* in current practice, a solution that can reduce the risk in the general population is needed. 100% Whey-Protein Partially Hydrolyzed formula, which is already widely available in the U.S. as a routine infant formula with cost and taste similar to standard intact cow's milk formula, is just such a solution.

In summary, and applying all five of Zeiger's criteria, a strong case can be made that PHF-W will have a significant impact in the general population of infants, as a safe intervention strategy for the primary prevention of atopic disease, when used in preference to intact cow's milk protein formulas in infants who are not being exclusively breast fed – and, all with no added cost from the intervention over other standard brand-name formulas.

REVIEW AND RATING OF THE SCIENTIFIC EVIDENCE

Nature of the Supporting Scientific Evidence

Randomized, controlled, intervention studies comprise the bulk of the scientific evidence documenting the role of 100% Whey-Protein Partially Hydrolyzed formula in reducing the risk of allergy in healthy infants. This evidence is reported in a total of 18 published peer-reviewed clinical trial reports in 12 distinct cohorts of healthy infants. The majority of these studies have been conducted in at-risk populations defined by family history. That being said, there are published peer-reviewed trials that have recruited infants from the general population as well (Exl 2000, Exl 1998, Iikura 1995), and there are a few trials that have not been published in peer-reviewed journals, all of which had results consistent with, and corroborative of, those in the peer-reviewed publications. All of the peer-reviewed published trials focused on the exclusive feeding of formula either as the sole source of nutrition or in addition to breast milk. With the exception of one study (Willems 1993), all required this type of feeding for a minimum period of 4 months (Willems 1993 required exclusive feeding for 3 months). The studies differ in the formulas fed to comparison groups. As one would expect, investigations have focused on comparisons of 100% Whey-Protein Partially Hydrolyzed formulas (PHF-W) vs. standard cow's milk formula, extensively hydrolyzed formulas (EHF, both casein and whey-based), and/or soy formulas. Breastfed infant populations are also often included as comparison groups. In addition to the array of controlled, intervention studies involving PHF-W, the literature contains a number of reviews that discuss the role of hydrolyzed formulas in reducing the risk of developing allergy. Recent reviews are most helpful here because PHF-W were introduced long after extensively hydrolyzed formulas had been available.

As the reports of the controlled, intervention studies and the reviews reveal, difficulties attend not only the conduct, but also the interpretation of results from clinical investigations in infants. For example, a pure randomization scheme is impossible in trials that include breastfed infants. A mother must be allowed to choose whether to breastfeed or formula-feed her baby. As a result, comparisons made between formula-fed groups and breastfed groups cannot reasonably be based on randomized groups. Moreover, a number of confounding factors may exist between formula-fed and breastfed groups. Further complications arise in the context of blinding. This is especially the case when comparisons involve extensively hydrolyzed formulas. Although the infant is unaware of the type of formula being fed, the caregiver is often able to differentiate between the different formulas on the basis of taste and smell, especially if one of the formulas is an EHF. The caregiver's attitude toward the formula has the potential to bias the information that is shared with the physician.

The reported investigations also differ in the symptoms of allergy used as measures of outcome. Dermatological, respiratory, and gastrointestinal manifestations are not uniformly identified or stressed. Furthermore, although clinical examination is always part of the diagnosis of allergy in the reported investigations, the laboratory tests employed in the diagnosis differ as do the nature of the food challenges (*e.g.,* open or double-blind, placebo-controlled).

Although double-blind placebo controlled food challenges are generally viewed as the standard for confirming the etiology of allergic symptoms, such food challenges may present obstacles in clinical practice and for clinical studies. They require much more time and intervention for the medical professionals and participants. Particularly with infant subjects, they present ethical issues as well. As a result, double-blind, placebo-controlled food

challenges (DBPCFC) are rarely employed in infant allergy prevention studies. Open food challenges, skin prick tests, and clinical examinations are the diagnostic tools most often used in these trials.

The following sections highlight select publications of some of these trials. Appendices C-II and C-III contain summaries of all published peer-reviewed and non peer-reviewed studies, respectively, that compare PHF-W and intact cow's milk formula (CMF) in allergy prevention. In virtually all of these investigations, the PHF-W included has been one of the international counterparts of NESTLÉ GOOD START SUPREME (Good Start HA, Nativa HA, Nidina HA, Nan-HA, Beba HA).

Strength of the Association between PHF-W and Allergy Prevention

Eighteen peer-reviewed reports of controlled intervention trials in 12 population cohorts have been published comparing the use of Nestlé PHF-W to standard CMF on the development of allergy in healthy infants. In addition, studies of allergy prevention in six other population cohorts have been presented in abstract form, at international meetings or as theses. Of the 12 cohorts evaluated in trials using Nestlé PHF-W that have been in peer-reviewed publications, eight were randomized, controlled intervention trials (Design Type 1). The remaining four studies were nonrandomized intervention trials with concurrent controls (Design Type 3). Half of these studies have received a '+' rating for adequately addressed issues of scientific quality, while the other six have some uncertainties regarding the randomization and/or blinding involved (∅). These design-type classifications and quality ratings are incorporated into the summary tables in Appendices C-II and C-III, and they follow the "rating" methods described in FDA's July 10, 2003 Guidance entitled "Interim Evidence-based Ranking System for Scientific Data".

Each study is unique, using various group comparisons, diagnostic procedures, study designs and interventions; each one fulfills the AAP criteria for an allergy prevention trial to differing degrees. According to the AAP, allergy prevention trials should be randomized, controlled studies in infants from families with a history of allergy where allergic responses are established prospectively, evaluated with validated scoring systems and confirmed by DBPCFC with a minimum follow-up of 18 months (preferably up to 72 months; AAP 2000). Particularly persuasive in addressing design issues and evaluating the prevention effect of PHF-W is the independent GINI study (Von Berg 2003). This is the largest, randomized, controlled intervention study (double-blind, multi-center) of its kind. Prior to the initiation of this study, the leading experts of pediatric allergy were consulted for input into its design. The 1-year results support the role of PHF-W in reducing the incidence of atopic dermatitis in healthy high-risk infants and indicate differential effects of the formulas in infants without genetic predisposition to specific allergy symptoms. Although not yet published, the 3-year data have been presented at the European Academy of Allergology and Clinical Immunology (EAACI) meeting (2003) and other national and international meetings and are consistent with the results of long-term follow-up studies in other subject cohorts in demonstrating a reduction in the risk of atopic disease. A 6-year follow-up on the GINI cohort is also planned.

The implications of the substantial body of literature regarding the use of PHF-W in allergy prevention are seen in the published calculations of meta-analyses by Osborn and Sinn (2003) and Baumgartner and colleagues (1998). Osborn, on behalf of the Cochrane Library, assessed all the available literature on the use of hydrolyzed protein formulas for prevention of allergy, and published his conclusions in 2004: "In high risk infants [infants with a positive family history of allergy], who are unable to be completely breast-fed, there is evidence that prolonged feeding with a hydrolysed, compared to cow's milk formula reduces

infant and childhood allergy and infant [cow's milk allergy]." This analysis goes on to conclude that "Further trials are required to determine if significant clinical benefits persist beyond five years of age and if there is any additional benefit from use of an extensively compared to a partially hydrolysed formula. Incremental costs of formula and the effect on compliance should be measured."

Osborn and Sinn report that to prevent one case of childhood allergy the number of high-risk infants needed to treat (i.e., to exclusively feed with a hydrolysate formula) is four (2003). (Please note that "needed to treat" is used here as a statistical term, only, and does not imply any reference to "treatment" in a clinical sense.) Similarly, in a meta-analysis by Baumgartner and colleagues (1998), it was estimated that between three and five high-risk infants would need to be fed PHF-W to prevent the development of allergy in one infant. Both meta-analyses using several of the studies discussed in this petition showed that use of PHF-W can reduce the incidence of allergy in comparison to CMF.

Currently, the AAP recommends the use of a hypoallergenic (i.e., EHF) formula or *possibly* a partial hydrolysate in high-risk infants for primary prevention of food allergy, when not breastfeeding (2000). Further growth in the body of evidence since the time of the August 2000 AAP statement, and particularly the publication of the 1-year Von Berg results (2003), strengthens the role of PHF-W in allergy prevention. While extensively hydrolyzed formulas are more generally accepted in the role of primary prophylaxis of allergy, their greater expense and lesser palatability are limiting. Furthermore, studies have shown PHF-W to be similar to EHF in terms of allergy prevention (Osborn 2003, Von Berg 2003, Nentwich 2001, Halken 2000, Porch 1998). Combined with the unpredictability as to which infants will actually develop allergy, routine PHF-W use for the purpose of primary prevention of allergy is a logical intervention for the general population of non-breastfed infants.

Weight of Credible Evidence

The evidence in support of the proposed claim is based on the consistent results observed in the numerous published clinical trials on the impact of PHF-W on allergy prevention. Regardless of the various types of study design and outcomes assessed, PHF-W has been shown to be superior to standard CMF, with varying degrees of statistical significance, in reducing the risk of allergy. All studies demonstrate a decrease in allergy symptoms (cumulative incidence) with PHF-W compared to CMF. No study has shown the contrary, with or without statistical significance. Although the majority of studies have been done in healthy populations with a family history of allergy, a beneficial effect of PHF-W consumption on allergy prevention has also been observed in the general population as noted in the Exl (1998) and Iikura (1995) publications. The results of Von Berg (2003) also point towards the use of PHF-W in infants without family history of specific atopic symptoms, as a reduction in atopic dermatitis was observed in this subset of infants. Taken together, studies discussed within this petition lead to the conclusion that dietary intervention including PHF-W plays a role in the prevention of allergy for as many as 5 years after the period of exclusive feeding.

Even though the numerous studies published and/or presented had some variation in design and specific interventions, they all consistently demonstrate that using PHF-W for formula-fed infants can decrease the cumulative incidence of allergy and reduce allergic symptoms as compared to standard cow's milk formula. No study has shown that infants fed PHF-W had a higher incidence of allergy when compared to infants fed standard whole-protein cow's milk. The overview graphs in Appendix C-II depict the consistent results seen in the published, peer-reviewed reports of studies, as well as those studies presented or published in non-peer reviewed documents, investigating the use of PHF-W as a means of

allergy prevention compared to CMF. Bar graphs of the cumulative incidence of allergic manifestations and atopic dermatitis show how all studies resulted in decreased incidence in the PHF-W group. Odds ratios based on these studies are also depicted, again showing the allergy preventive effect of PHF-W compared to standard intact cow's milk formulas. The consistent results seen in this body of allergy prevention studies confirm a role for PHF-W in allergy prevention in infants.

To address the potential of publication bias, following an extensive search, all studies identified from non-peer reviewed sources are included as part of the supportive evidence. The results reported in these studies are completely consistent with those published in peer reviewed journals: for all those where cumulative incidences and odds risk ratios were possible to calculate, PHF-W reduced the incidence and risk of allergy compared to intact protein formulas, with varying degrees of statistical significance. Similarly also, no study reported, with or without statistical significance, an increase in allergy incidence.

Nestlé's estimated overall rating and ultimate ranking of "***" in FDA-proposed terminology for the consistency, quality and relevance of the entire body of data, is illustrated by the discussion in the following pages and supported by the availability of several corroborative meta-analyses and other review papers. The Company believes this evidence comes as close as possible, given the limitations inherent to allergy studies in infants, to establishing a basis for the "significant scientific agreement" standard required of an *unqualified* health claim. Nestlé, as well as the many experts with whom the Company has consulted on this issue, believe the propriety of such a claim is established by the weight of credible evidence, including the unquestionably independent confirmation by the GINI study of years of previous research. Nestlé recognizes, however, the time-dependant, evolutionary character of allergy investigation and of scientific consensus with respect to the meaning of

the results of such investigation. In this context, the Company also recognize the novelty and importance of a health claim associated with infant formula, and that good science and regulatory stewardship suggest caution in proceeding. Under these circumstances, Nestlé is requesting agency review for the highest possible level of *qualified* health claim instead. Nestlé believes a qualified health claim is in the public interest, will provide meaningful, scientifically sound, and truly helpful information to caregivers and physicians, and will foster scientific interest and further research in this important arena.

CERTIFICATION OF ETHICAL COMPLIANCE

In accordance with 21 CFR § 101.70(c) and 21 CFR § 170(d) Nestlé declares that to the best of our knowledge, all non-clinical studies relied upon in our petition were conducted in compliance with the good laboratory practice regulations as set forth in 21 CFR Part 58, and all clinical or other human investigations relied upon were either conducted in accordance with the requirements for institutional review set forth at 21 CFR Part 56 or were not subject to such requirements in accordance with 21 CFR §§ 56.104 or 56.105, and were conducted in conformance with the requirements for informed consent set forth in 21 CFR Part 50.

REVIEW OF SELECTED CLINICAL TRIALS

The six studies which received a quality factor of '+' are discussed in detail in the following pages. And, while the FDA scoring system for design-type and quality ratings were used for this ranking analysis, a scoring system developed by Nestlé, and focusing on the integrity or validity of the studies, was used to determine the order in which these six studies are presented here, with the highest-scoring study presented first, and the others following in descending order (See Appendix C-VI for an explanation of the Nestlé Scoring System). A short discussion of meta-analyses, review papers and non-peer-reviewed reportsfollows those

detailed reviews. The entire body of published data, peer-reviewed and non-peer-reviewed, is summarized in graphic and tabular format in the Appendices that follow these narrative discussions.

Appendix C-II is the Summary Table of all prospective, peer-reviewed, published studies involving PHF-W and CMF and allergy prevention. Appendix C-III is the Summary Table of all Non-peer reviewed studies comparing PHF-W to CMF. Both Summary Tables include a rating of the studies according to the FDA Guidance criteria. Appendix C-V is the Summary Table of the meta-analyses as well as select review papers. Appendix C-VI is a description of the Nestlé Scoring System used to determine the order of presentation for the study summaries. References to all of the studies mentioned in this Summary of Scientific Data (as well as those mentioned in other sections of this Petition) are included in Section H of Volume I. Reprints of all relevant and available references are enclosed in Volume II.

Von Berg 2003

Von Berg A, Koletzko S, Grübl A, Filipiak-Pittroff B, Wichmann H, Bauer CP, Reinhardt D, Berdel D, German Infant Nutritional-Intervention Study Group. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. J Allergy Clin Immunol 2003;111:533-40.

Study Design

The objective of this randomized, controlled intervention trial (double-blind, multi-center) was to assess the preventive effect of different hydrolyzed formulas as compared to standard cow's milk formulas (CMF) in healthy high-risk infants. "High-risk" was defined as encompassing infants with at least one first-degree relative with an allergic disease. At inclusion, infants were randomized to one of four coded formulas: a partially hydrolyzed whey formula (PHF-W), CMF, an extensively hydrolyzed casein formula (EHF-C), or an extensively hydrolyzed whey formula (EHF-W). All mothers were encouraged to breastfeed for at least 4 months, and preferably up to 6 months. Timing of weaning and introduction of study formula was at the parents' discretion. No solid foods were given during the first 4 months, and thereafter no more than one new food per week was introduced. Parental compliance was assessed based on diary entries and structured interviews. Subjects were seen at 1, 4, 8, and 12 months of age. Unscheduled visits were made when possible allergic symptoms appeared.

Outcome Measurements

Allergic manifestations (AM) defined as:

- Atopic dermatitis (AD)
- Urticaria
- Food allergy with manifestation in the gastrointestinal tract (FA-GIT)

Statistical Analysis

Effects on incidence of the outcome measurements were analyzed by means of simple logistic regression models. Multiple logistic regression models were used to adjust for potential risk factors and confounders. For the final model, adjusted odds ratios with 95% confidence intervals are reported.

Results

A total of 2252 infants were randomized to study formula. Within the first 4 weeks, 114 (5%) left the study before an examination. 889 (42%) infants were exclusively breastfed during the first 4 months. Out of the 1249 infants who received study formula, 166 children (13%) dropped out prior to the 12-month follow-up. An additional 138 children were excluded because of noncompliance. Therefore, a total of 945 infants were included in the per protocol analysis. Of the infants who adhered to the protocol, there were no significant differences among the 4 study formula groups in regards to feeding or baseline characteristics, family history of allergies, and sociodemographic data.

Of the 945 infants who consumed study formula, 119 (13%) had allergic manifestations during the first year of life, with atopic dermatitis being the most prevalent. Atopic dermatitis was diagnosed in 106 (11%), allergic urticaria in 5 (0.5%), and manifestations in the GI tract occurred in 12 infants (1.3%). At 12 months, the incidence of allergic manifestations was significantly lower in infants fed EHF-C compared to CMF ($p = 0.025$) whereas the reduction seen in the PHF-W ($p = 0.114$) and the EHF-W ($p = 0.544$) did not reach significance.

First-year incidence of AD, allergic urticaria, FA-GIT, and AM with crude odd ratios from logistic regression dependent on the feeding regimen.

	CMF	**PHF-W**	**EHF-C**	**EHF-W**
Number of subjects	256	241	210	238
AD				
n	38	22	15	31
%	14.8	9.1	7.1	13.0
Urticaria				
n	1	0	3	1
%	0.4	0.0	1.4	0.4
FA-GIT				
n	1	5	4	2
%	0.4	2.1	1.9	0.8
AM				
n	40	26	19	34
%	15.6	10.8	9.1	14.3
Crude odds ratio	1	0.65	0.54	0.90
95% CI		(0.39 – 1.1)	(0.30 – 0.96)	(0.55 – 1.5)
p-value		0.114	0.036	0.677

Multiple logistic regression models were used to adjust for sex ($p = 0.037$), atopic dermatitis in the family ($p < 0.001$), and maternal smoking after birth ($p = 0.015$). After adjusting the effects of the feeding regimens on the incidence of allergic manifestations, EHF-C was the only formula with a significant ($p = 0.025$) protective effect. However, if only atopic dermatitis was considered as the outcome measurement, both EHF-C and PHF-W reduced the incidence of atopic dermatitis significantly ($p = 0.007$ and $p = 0.048$, respectively).

Data was stratified with respect to the presence of atopic dermatitis in the core family. When this was done, different effects of the formulas on the incidence of allergic manifestations and atopic dermatitis were observed. In infants without atopic dermatitis in the core family ($n = 603$), feeding hydrolysate formulas (PHF-W, EHF-C, and EHF-W combined) reduced the incidence of allergic manifestations as compared to the CMF group. This difference fell just short of statistical significance ($p = 0.054$).

Results of the multivariable models: adjusted odds ratio for AM and AD dependent on feeding regimen and stratified by AD in family history (FH)

			CMF	PHF-W	EHF-C	EHF-W
Allergic Manifestations	All	Incidence, n/N (%)	40/256 (16)	26/241 (11)	19/210 (9)	34/238 (14)
		Adjusted OR* (95% CI)	1	0.65 (0.38–1.1)	0.51 (0.28 – 0.92)	0.86 (0.52-1.4)
		p-value		0.109	0.025	0.544
	No AD in FH	Incidence, n/N (%)	22/165 (13)	14/162 (9)	10/134 (7)	11/142 (8)
		Adjusted OR† (95% CI)	1	0.63 (0.31-1.3)	0.51 (0.23-1.1)	0.55 (0.26-1.2)
		p-value		0.210	0.101	0.131
	AD in FH	Incidence, n/N (%)	18/91 (20)	12/79 (15)	9/76 (12)	23/96 (24)
		Adjusted OR† (95% CI)	1	0.72 (0.32-1.6)	0.53 (0.22-1.3)	1.3 (0.63-2.5)
		p-value		0.426	0.148	0.515
Atopic Dermatitis	All	Incidence, n/N (%)	38/256 (15)	22/241 (9)	15/210 (7)	31/238 (13)
		Adjusted OR* (95% CI)	1	0.56 (0.32-0.99)	0.42 (0.22-0.79)	0.81 (0.48-1.4)
		p-value		0.048	0.007	0.44
	No AD in FH	Incidence, n/N (%)	21/165 (13)	10/162 (6)	8/134 (6)	11/142 (8)
		Adjusted OR† (95% CI)	1	0.46 (0.21-1.02)	0.42 (0.18-1.00)	0.58 (0.27-1.3)
		p-value		0.055	0.050	0.173
	AD in FH	Incidence, n/N (%)	17/91 (19)	12/79 (15)	7/76 (9)	20/96 (21)
		Adjusted OR† (95% CI)	1	0.75 (0.33-1.7)	0.43 (0.17-1.1)	1.1 (0.54-2.3)
		p-value		0.494	0.077	0.757

FH = family history
* Adjusted for AD in family history, sex, and maternal smoking after birth
† Adjusted for sex and maternal smoking after birth

Authors' Relevant Conclusions

"Our findings raise the question of whether nutritional intervention, including breast-feeding, is less effective in infants with a stronger genetic background for AD."

"In conclusion, our results clearly indicate that feeding a hydrolyzed formula instead of CMF as a supplement or substitute to breast milk during the first 4 months of life reduces the risk of AM during the first year of life. However, the different hydrolysates do not offer the same degree of prevention. Our data show that neither the degree of hydrolysis nor the protein source is predictive of the preventive effect and that the genetic background might modify the preventive potential of a hydrolysate. Therefore the effect of each hydrolyzed formula aiming for prevention of AM needs to be clinically evaluated."

"Prevention of allergic diseases in the first year of life is feasible by means of dietary intervention but influenced by family history of AD. The preventive effect of each hydrolyzed formula needs to be clinically evaluated."

Nestlé Comments

To date, this is the largest, randomized, multi-center, double-blind trial comparing the effects of 3 hydrolyzed infant formulas to standard cow's milk formula on the incidence of

allergy in infants exclusively fed study formula for the first 4 months of life. This work is non-industry sponsored.

The investigators noted that a significantly ($p = 0.02$) greater number of children in the EHF-C group had to be excluded due to non-compliance. Although they did not explore this finding in greater detail, decreased palatability of the EHF-C may have played a role in acceptance of the product, either by the subject or by the subject's guardian.

The investigators also observed that the preventive potential of the different formulas was to some extent dependent on the family history (FH) of atopic dermatitis (AD). Such was not the case in the EHF-C group, where the incidence of AD was reduced to a similar degree with or without the presence of AD in FH (odds ratios of 0.43 and 0.42, respectively). It is interesting to note, however, that the whey-based formulas had distinctly different effects on the outcomes measured, depending upon the presence of a FH of AD. In the EHF-W group, the odds ratio was reduced from 1.1 in infants with a FH of AD to 0.58 in infants with no FH of AD. Similarly, for the incidence of AD within the PHF-W group, the odds ratio in infants with a positive FH of AD was 0.75 as compared to 0.46 in infants from families with no FH of AD. The reduction in incidence of AD in the PHF-W infants with no AD in FH approached statistical significance ($p = 0.055$). A similar observation can also be made in the incidence of allergic manifestations. This result demonstrates that family history of specific allergic symptoms is not necessarily predictive of allergy development in infants. Feeding strategies for the purpose of reducing the incidence of allergy appear to be useful even in subsets of infants who do not have a specific family history of atopic dermatitis.

	Atopic dermatitis	**CMF**	**PHF-W**	**EHF-C**	**EHF-W**
No AD in FH	Incidence, n/N (%)	21/165 (13)	10/162 (6)	8/134 (6)	11/142 (8)
	Adjusted OR† (95% CI)	1	0.46 (0.21-1.02)	0.42 (0.18-1.00)	0.58 (0.27-1.3)
	p-value		0.055	0.050	0.173
AD in FH	Incidence, n/N (%)	17/91 (19)	12/79 (15)	7/76 (9)	20/96 (21)
	Adjusted OR† (95% CI)	1	0.75 (0.33-1.7)	0.43 (0.17-1.1)	1.1 (0.54-2.3)
	p-value		0.494	0.077	0.757

The published 1-year follow-up results summarized here indicate exclusive feeding with PHF-W can help reduce the incidence of AD, the predominant allergic disease during infancy. The investigators have planned a 6-year follow-up. At the European Academy of Allergology and Clinical Immunology (EAACI) 2003 meeting in Paris, the 3-year results were presented. Although not yet published, the investigators' findings at 3 years were similar to the results at the 1-year follow-up, in demonstrating a reduction in the risk of atopic disease with PHF-W.

Vandenplas 1995

Vandenplas Y, Hauser B, Van den Borre C, Clybouw C, Mahler T, Hachimi-Idrissi S, Deraeve L, Malfroot A, Dab I. The long-term effect of a partial whey hydrolysate formula on the prophylaxis of atopic disease. Eur J Pediatr 1995;154:488-94.

Vandenplas Y, Hauser B, Van den Borre C, Sacre L, Dab I. Effect of a whey hydrolysate prophylaxis of atopic disease. Ann Allergy 1992;68:419-24.

Vandenplas Y. Atopy at 3 years in high-risk infants fed whey hydrolysate or conventional formula. Lancet 1992;339:1118. (non-peer reviewed)

Study Design

The objective of this randomized, controlled intervention trial (double-blind) was to determine the preventive effect in atopic disease of feeding a partially hydrolyzed whey infant formula (PHF-W) to infants at risk of allergy. Risk was defined as a minimum of two first-degree relatives with atopy. Mothers who chose to formula-feed were randomized to one of two formula groups (PHF-W or standard cow's milk formula (CMF)). The coded formulas were delivered in an unlabelled package. Infants were exclusively fed their assigned formula for 6 months, with the exception of a grated apple given daily to all infants from the age of 4 months on. At the age of 6 months, infants were allowed an unrestricted weaning diet, except in those who had developed symptoms suggestive of cow's milk protein sensitivity. Subjects were followed for 60 months, and data were reported at 6, 12, 36, and 60 months. Compliance was monitored by monthly exchanges of empty formula containers.

Outcome measurements

- Angioedema
- Asthma
- Atopic dermatitis
- Chronic cough
- Chronic rhinitis
- Gastrointestinal symptoms (recurrent colic, vomiting, and/or diarrhea)
- Urticaria

Laboratory testing:

- IgE (6 months)
- RAST
- SPT

Statistical analysis

Statistical analysis on the outcome measurements was performed using Fisher's exact probability test (unilateral).

Results

Seventy-five infants were included in this study. Fifty-eight infants (23% attrition rate) completed the 5-year follow-up and were analyzed. Data from children lost during follow-up were not considered. Results reported here are based on the 1995 publication. Therefore, earlier publications from this study may have larger sample sizes than reported

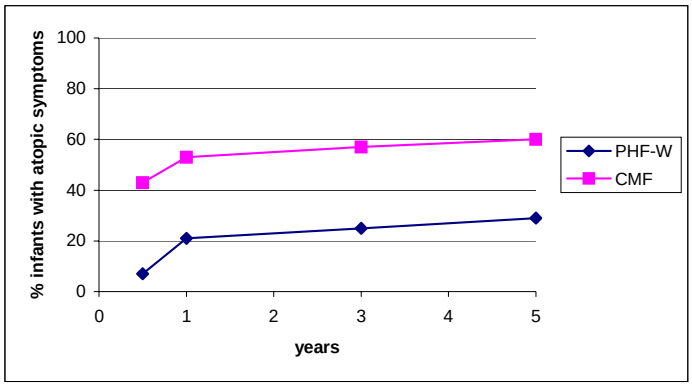
here, as the publication of the 5-year follow-up only reports on the 58 infants completing all visits.

When calculated cumulatively, the number of children with atopic manifestations at 5 years was significantly lower (p = 0.016) in the PHF-W group than the CMF group.

Number of infants with atopic symptoms (including diarrhea and colic as a single manifestation).

Period (months)	PHF-W (n = 28)		CMF (n = 30)		p-value
	n (%)	(conf limit)	n (%)	(conf limit)	
0 – 6	2 (7%)	(0.9 – 23.5)	13 (43%)	(25.5 – 62.6)	0.002
0 – 12	6 (21%)	(8.3 – 40.9)	16 (53%)	(34.3 – 71.7)	0.029
0 – 36	7 (25%)	(10.7 – 44.9)	17 (57%)	(37.4 – 74.5)	0.018
0 – 60	8 (29%)	(13.2 - 48.7)	18 (60%)	(40.6 – 77.3)	0.016
6 – 12	6 (21%)	(8.3 – 40.9)	5 (17%)	(5.6 – 34.7)	NS
12 – 36	5 (18%)	(6.1 – 36.9)	8 (27%)	(12.3 – 45.9)	NS
36 – 60	3 (11%)	(2.3 – 28.2)	4 (13%)	(3.8 – 30.7)	NS
6 – 60	7 (25%)	(10.7 – 44.9)	9 (30%)	(14.7 – 49.4)	NS

Cumulative incidence of percentage of infants with atopic symptoms over the first 5 years



Authors' Relevant Conclusions

"If mother's milk is not available and other studies confirm these results, there might be an indication for partial hydrolysates in infants with a family history of atopy, since these formulae reduce the incidence of CMP sensitivity."

"It is concluded that the use of a partial whey hydrolysate in a high risk population decreased the prevalence of eczema, and the incidence of diarrhoea during the first 6 months of life."

Nestlé Comments

This study focuses on a single intervention (early feeding regime) in the prevention of cow's milk protein sensitivity and supports both the allergy-prevention effect of PHF-W during the period of active feeding and the long-term beneficial effects of such an intervention, even after diet diversification.

The 6-and 12- month (1992) data as well as the 5-year (1995) data have been published in peer-reviewed journals. The 3-year data were published in the form of a non-peer reviewed letter (1992).

With a sample size of 75 infants and having 58 subjects complete the 5-year follow-up, this study involved a relatively small population. While this study has a small sample size, the direction of the results is consistent with larger published studies.

Marini 1996

Marini A, Agosti M, Motta G, Mosca F. Effects of a dietary and environmental prevention programme on the incidence of allergic symptoms in high atopic risk infants: three years follow-up. Acta Paediatr Suppl 1996;414:1-21.

Study Design

The objective of this randomized, controlled, intervention trial (single-blind, multi-center) was to evaluate the effectiveness of exclusive and prolonged feeding with partially hydrolyzed whey infant formula (PHF-W) within the context of a dietary prevention program in healthy infants at high-risk for developing atopy. High-risk infants were defined as having biparental allergy. Parents self-selected to an "intervention" or "non-intervention" diet group.

Infants within both groups were breastfed for varying periods of time up to four months. In the non-intervention group, mothers made their own choices regarding the introduction of formula. Weaning was as indicated by personal pediatrician, both for timing and types of food.

Within the intervention group, subjects were randomly assigned to one of two formulas: PHF-W or a standard cow's milk formula (CMF). Subjects were exclusively fed the assigned formula for five months. Intervention also included diet restriction for breastfeeding mothers, along with encouragement to breastfeed for a longer period. No solid foods were allowed until five months of age and then included cereals, vegetables, Parmesan cheese, olive oil, meat and fruit. In addition, the intervention group also received environmental instructions, advising avoidance of smoking, keeping no furry pets, frequent cleaning of carpets, and keeping the infant out of an infant community until 2 years of age.

In both groups subjects were followed for 36 months and were seen at 3, 6, 12, 24 and 36 months. A blinded physician confirmed the diagnosis of allergic symptoms.

Outcome Measurements:

- Allergic rhinitis and conjunctivitis
- Atopic dermatitis
- Gastrointestinal symptoms
- Recurrent wheezing
- Urticaria

Laboratory testing:

- IgE at birth, 12, 24 months
- Following allergy diagnosis, RAST during the first year of life
- For rhinitis, conjunctivitis, recurrent wheezing, SPT in second and third year of life

Statistical Analysis

Statistical analysis included Fisher's exact test and Student's t-test. For variables that were not normally distributed, Wilcoxon's test and Mann-Whitney's test were used.

Results

For this study, 359 infants were enrolled. From this group of healthy high atopic risk infants, 80 chose to be in the non-intervention group. The remaining 279 infants were randomized to one of two formula groups to use if breastfeeding was insufficient.

Intervention n = 279		**Non-intervention n = 80**	
Breast (diet control)	124	Breast > 4 mos	40
Breast + CMF	28	Breast + CMF	21
Breast + PHF-W	32		
PHF-W	48		
CMF	47	CMF	19

At 3 years, the attrition rate for the intervention group was 20.1%; for the non-intervention group, the rate was 22.5%.

The incidence of allergic manifestations was lower in the intervention group as compared to the non-intervention group at 1 year (11.5% versus 54.4%, respectively), at 2 years (14.9% versus 60.1%) and at 3 years (20.6% versus 74.1%). No p-values are reported for these comparisons.

Cumulative incidence of atopic symptoms

	Intervention	**Non-intervention**
1 yr	28/243 (11.5%)	37/68 (54.4%)
2 yr	35/234 (14.9%)	39/64 (60.1%)
3 yr	46/223 (20.6%)	46/62 (74.1%)

Within the intervention group, the breastfed and PHF-W groups had a lower cumulative incidence of allergic manifestations (both overall and for each individual symptom) as compared to the CMF group at 1,2 and 3 years of age. The mixed feeding groups (Breast + PHF-W and Breast + CMF) showed an intermediate incidence of allergic symptoms.

Intervention group: Incidence of atopic symptoms by specific feeding group

	Breast	**PHF-W**	**CMF**	**Breast+PHF-W**	**Breast+CMF**
1 yr	9/108 (8.3%)	3/43 (6.9%)	8/41 (19.5%)	4/28 (14.2%)	4/23 (17.3%)
2 yr	11/104 (10.5%)	5/42 (11.9%)	11/40 (27.5%)	4/26 (15.3%)	4/22 (18.2%)
3 yr	13/98 (13.2%)	7/40 (17.5%)	16/38 (42.1%)	5/25 (20%)	5/22 (22.7%)

RASTs were positive in 24/46 subjects, especially in cases of atopic dermatitis (22/27). SPT were positive in13/18 subjects with seasonal rhinitis-conjunctivitis and recurrent wheezing in the second year. At birth, there was no difference among the groups in total IgE levels in the intervention group. At 1 and 2 years, the breastfed group had significantly lower total IgE level as compared to CMF.

Authors' Relevant Conclusions

"Breastfed babies (with a hypoallergenic diet for the mother), babies fed on the hydrolysed formula, and those fed on a combination of breast milk and hydrolysed formula had the lowest incidence of allergic manifestations. This was confirmed by multivariate analysis."

Nestlé Comments

At 1 and 2 years, the cumulative incidence of allergic manifestations was significantly lower in both the breastfed and PHF-W group as compared to the CMF group. At 3 years, the authors stated the cumulative incidence was significantly lower in the breastfed (13.2%) group as compared to the CMF (42.1%) group. No mention was made of any statistical significance of the comparison of either CMF or breastfed to PHF-W at 3 years, but it was evident that the cumulative incidence with PHF-W at that point (17.5%) was much closer to that of the breastfed group than of the CMF group. For comparisons within the Intervention group, the investigators do not list any p-values.

This was a single-blinded trial. Mothers were not blinded to formula allocation. As the mothers were aware of which formula their infant was consuming (and obviously if she was breast-feeding), it is possible that the mother may have shared this information with the study pediatrician. However, the attending physician who confirmed the allergy diagnosis was blinded to the dietary regimens involved in this study.

Chandra 1997

Chandra RK. Five-year follow-up of high-risk infants with family history of allergy who were exclusively breast-fed or fed partial whey hydrolysate, soy, and conventional cow's milk formula. J of Pediatr Gastroenterol Nutr 1997;24:380-8.

Chandra RK, Hamed A, Prasad C, Singh GK. Cumulative incidence of allergic disorders in high risk infants fed whey hydrolysate, soy, and conventional cow's milk formulas. Am J Clin Nutr 1992;56:758 (Abstract).

Chandra RK, Hamed A. Cumulative incidence of atopic disorders in high risk infants fed whey hydrolysate, soy, and conventional cow milk formulas. Ann Allergy 1991;67:129-32.

Chandra RK, Singh G, Shridhara B. Effect of feeding whey hydrolysate, soy and conventional cow milk formulas on incidence of atopic disease in high risk infants. Ann Allergy 1989;63:102-6.

Study Design

The objective of this randomized, controlled intervention trial (double-blind) study was to assess the effect of feeding different infant formulas on the incidence of atopic disease and food allergy in healthy high-risk infants. High-risk infants were defined as having at least one first-degree relative with atopic disease.

A self-selected breastfed control group was included. Infants were exclusively fed breastmilk for 4 months. Mothers who chose not to breastfeed were randomly assigned to one of three coded formulas: a partial whey hydrolysate (PHF-W), conventional cow's milk formula (CMF), or soy-based formula (Soy). Subjects were exclusively fed their assigned formula for the first six months and followed until five years of age. After the age of 6 months, infants were fed according to the general advice regarding weaning given to all families with history of allergy. Data collection intervals were 6, 12, 18 months, 3 and 5 years.

Outcome Measurements

- Atopic eczema
- Asthma

Laboratory tests

- SPT
- DBPCFC (performed for symptomatic children; Food allergens tested include milk, soy, egg, peanut, fish, wheat, corn, orange, banana, chicken.)

Statistical Analysis

Prevalence and incidence data were tested by multiple comparison and two-group comparisons using Chi square test with corrections as required. If data were not normally distributed, the nonparametric Kruskal-Wallis test of multiple comparisons was used; for two-group comparisons, the Mann-Whitney Rank Sum test was used.

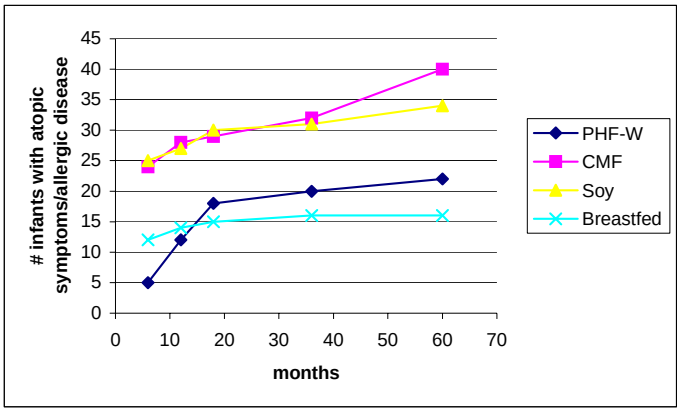
Results

From the publication of the 5-year data (1997; Tables 4 and 6), of the 288 infants enrolled, 263 infants completed the study (9% attrition rate). Similar to published observations from 6 and 18 months, the cumulative incidence of clinical allergic disease until 5 years of age was significantly lower in the PHF-W group as compared to CMF ($p = 0.0014$) and Soy ($p < 0.05$). The cumulative incidence in the PHF-W group was not significantly ($p > 0.1$) different than the breastfed group.

Cumulative incidence of allergic disease in high-risk infants followed until 5 years of age

Group	Number of affected subjects (%)	Odds-ratio (95% ratio)
CMF (n = 67)	40 (60%)	1.0
PHF-W (n = 68)	22 (37%)	0.322 (0.159-0.653)
Soy (n = 68)	34 (50%)	0.759 (0.384-1.501)
Breast (n = 60)	16 (27%)	0.422 (0.200-0.891)

Cumulative incidence of allergic disease at the age of 6, 12, 18, 36 and 60 months*



*Graph depicts combination of data from all publications, including 1992 abstract (36 mo).

Of the formula-fed infants, those fed PHF-W had the least incidence of eczema at all observation points (PHF-W versus CMF, $p < 0.05$; PHF-W versus Soy, $p > 0.05$). Among the infants affected with eczema, the severity was lowest in the PHF-W group compared to CMF ($p = 0.002$) and soy ($p = 0.01$). There was no difference in eczema score between PHF-W and the breastfed group.

Regarding the cumulative incidence of asthma, PHF-W had the lowest incidence as compared to CMF ($p < 0.05$), and was also lower, but not significantly, than the Soy group. There was no difference in cumulative incidence of asthma between PHF-W and the breastfed group.

Based on DBPCFC, the incidence of food allergy in the PHF-W group was significantly decreased as compared to CMF and Soy.

Positive skin prick tests and positive double-blind placebo-controlled food challenges*

Age / feeding group	Total Number	Total Number Symptomatic	SPT	DBPCFC
1-6 months				
PHF-W	68	5	4	3[b]
CMF	67	24	16	12[a]
Soy	68	25	19	14[a]
Breast	60	12	10	2[b]
7-12 months				
PHF-W	68	12	9	6[d]
CMF	67	28	24	16[c]
Soy	68	27	22	17[c]
Breast	60	14	12	8[d]
13-60 months				
PHF-W	68	22	16	9[f]
CMF		40	36	24[e]
Soy	68	34	29	19[e]
Breast	60	16	14	8[f]

*Within each age group, numbers with different superscript letters differ significantly from each other. 1-6 mo: PHF-W versus CMF, p = 0.016; PHF-W versus Soy, p = 0.004; 7-12 mo: PHF-W versus CMF, p = 0.018, PHF-W versus Soy, p = 0.012; 13-60 mo: PHF-W versus CMF, p = 0.003, PHF-W versus Soy, p = 0.036

Authors' Relevant Conclusions

1997: "Exclusive breast-feeding or feeding with a partial whey hydrolysate formula is associated with lower incidence of atopic disease and food allergy. This is a cost-effective approach to the prevention of allergic disease in children."

1997: "In conclusion, effective long-term prevention of atopic eczema and asthma among infants with family history of allergy can be achieved by feeding a partial whey hydrolysate formula for the first 6 months of life. Because the cost of such a formula for prophylaxis is almost comparable to that of standard cow's milk formulas, improving atopic symptoms and food allergy in high-risk infants who are not breast-fed can be accomplished without increasing health care costs, which is an important practical consideration (ref)."

Nestlé Comments

While having a number of strengths, including use of double-blinded placebo controlled food challenges and length of follow-up, this study is a single center study, conducted in a geographically isolated region.

The cumulative incidence of allergy in the CMF group (60%) is higher than has been previously reported.

The 6- (1989), 12- and 18-month (1991) data as well as the 5-year (1997) data have been published in peer-reviewed journals. The 3-year (1992) data were published in abstract form.

Becker 2004

Becker A, Watson W, Ferguson A, Dimich-Ward H, Chan-Yeung M. The Canadian asthma primary prevention study: outcomes at 2 years of age. J Allergy Clin Immunol 2004;113:650-6.

Chan-Yeung M, Manfreda J, Dimich-Ward H, Ferguson A, Watson W, Becker A. A randomized controlled study on the effectiveness of a multifaceted intervention program in the primary prevention of asthma in high-risk infants. Arch Pediatr Adolesc Med 2000;154:657-63.

Study Design

The objective of this randomized, controlled intervention trial (single-blind, two-center) was to assess the preventive effect of a multifaceted intervention that included the use of a partially hydrolyzed whey formula (PHF-W) for the primary prevention of asthma in healthy high-risk infants. High-risk was defined as infants with at least one first-degree relative with asthma or two first-degree relatives with other IgE-mediated allergic diseases. At inclusion, mothers were prenatally randomized to the intervention group or the control group receiving usual care. Both groups were encouraged to breastfeed. Where breastfeeding was not possible, mothers in the intervention group were instructed to use PHF-W. The intervention also consisted of house dust mite control with pet and smoke avoidance. Further, in the intervention group, during the last trimester of pregnancy, mothers excluded nuts and seafood from their diets and received instruction to delay the introduction of solids to their infants until 6 months of age with the exclusion of cow's milk, seafood and peanuts for the first year of life. Home visits were carried out before the birth of the infant and at weeks and 4, 8, 12, 18, and 24 months after birth. At 12 and 24 months, each subject was seen by a blinded pediatric allergist for assessment.

Outcome Measurements

- Asthma (possible or probable)
- Recurrent wheeze
- Rhinitis without colds
- Skin prick tests

Statistical Analysis

Odds ratios with 95% confidence intervals were estimated and adjusted for maternal education and child's sex. A procedure for repeated measurements data was conducted to adjust for between- and within- subject variation resulting from the 12- and 24- month time points for each subject.

Results

A total of 545 healthy high-risk infants were enrolled in the study. Of the 278 subjects randomized to the intervention group, 251 completed the 12-month check-up with 246 of the subjects completing the 24-month assessment (88% attrition rate at 24 months). Of the 242 subjects randomized to the control group, 267 were available for assessment at 12 months with 230 completing the 24-month check-up (86% attrition rate at 24 months). From birth, a high proportion of mothers in both groups breastfed their infants (93% in the intervention group and 92% in the control group). At 8 months, a significantly greater percentage of intervention mothers were still breastfeeding as compared to the control group (61% vs 50%).

In the control group, 8.3% of the infants were given partially hydrolyzed formula. In the intervention group, 2.8% of infants were given cow's milk at some time during the first 12 months of life.

At 12 months of age, the risks for possible or probable asthma and rhinitis without colds were significantly reduced in the intervention group by 34% and 49%, respectively. There were no differences in the incidence of positive skin test results to inhalant allergens.

At 24 months of age, the intervention group had a significantly lower prevalence of asthma than the control group (16.3% vs. 23.0%). Similarly, there were significantly fewer children with recurrent wheeze in the intervention group compared to the control group. There was no difference in the incidence of positive skin test responses to at least one of the common allergens tested.

Prevalence of asthma at year 1 and 2

Months	Control group	Intervention group	Adjusted* Odds Ratio [95% confidence interval]
12	20.0%	15.5%	0.68 [0.42-1.09]
24	23.0%	16.3%	0.60 [0.37-0.95]

*Adjusted for differences in maternal education and sex of the child.

Authors' Relevant Conclusions

Chan-Yeung 2000: "In summary, the multifaceted intervention program instituted just before birth resulted in a modest but significant reduction in the relative risk of possible or probable asthma by 34% and rhinitis without colds by 49% at the age of 12 months in high-risk infants but failed to reduce the incidence of sensitization to inhalant allergens."

Becker 2004: "This multifaceted intervention program during a window of opportunity in the first year of life was effective in preventing asthma in high-risk children at 2 years of age. Future studies with this cohort at school age are important."

Nestlé Comments

This study was not designed to assess the effects of specific formulas on allergy prevention, but rather was an effort to demonstrate the value of a multi-faceted intervention program in the primary prevention of asthma. Given the use of multiple methods of intervention, the effect of single interventions cannot be evaluated.

The investigators focused on the outcome and diagnosis of asthma and did not assess atopic dermatitis, which would be the most common manifestation of food allergy.

The authors note that both the intervention and non-intervention groups had a higher than average amount of education. Consistent with other studies, this factor resulted in a high rate of breastfeeding. At 8 months even in the non-intervention group 50% of the mothers were still breastfeeding. The authors do not provide a further breakdown of the amount or duration of breastfeeding or formula exposure in the two groups. The authors do note that 8.3% in the non-intervention group received a PHF-W.

The results of the study support the use of PHF-W, when breastfeeding is not possible, as part of a program for primary prevention of allergy in healthy high-risk infants.

Chan 2002

Chan YH, Shek LPC, Aw M, Quak SH, Lee BW. Use of hypoallergenic formula in the prevention of atopic disease among Asian children. J Paediatr Child Health 2002;38:84-88.

Study Design

The objective of this randomized, controlled intervention trial (single-blind) was to assess the effectiveness of a partially hydrolyzed whey formula (PHF-W) on the development of atopic clinical manifestations and serum IgE levels in healthy high-risk infants. High-risk was defined as infants with at least one first-degree relative with a positive family history of atopy (asthma, eczema, or allergic rhinitis). Only infants whose parents chose not to breastfeed were considered for inclusion in the study. At inclusion, infants were randomized to receive either PHF-W or intact cow's milk formula (CMF) exclusively for the first four months of life. After four months, infants were allowed a weaning diet with no restrictions except for the type of formula given. Subjects were seen at 1, 3, 4, 5, 9, 12, 18 and 24 to 30 months of age.

Outcome Measurements

- Atopic eczema
- Urticaria
- Wheezing

Statistics

For each outcome, the cumulative occurrence at each time point was compared between the two groups using the Chi-squared test for association. Age at atopy presentation was analyzed using Kaplan-Meier survival functions and log rank statistics.

Results

Initially, 76 infants were randomized to receive PHF-W and 77 infants to the CMF group. At 30 months of age, 53 (70%) infants in the PHF-W group and 57 infants in the CMF group (74%) completed the study. There were no differences in sex, socioeconomic status, or anthropometrics between the two groups.

There was a significantly lower occurrence of eczema in the PHF-W group up to 24 months of age. While the occurrence was lower in the PHF-W group at 30 months compared to the CMF group, this difference did not reach significance (p=0.090). The occurrence of wheezing in the PHF-W group was lower than the CMF group at all time points, although the difference was not significant (p=0.053-0.494). Only one subject in the PHF-W group had urticaria at 24 months that resolved within a month. There were no differences in serum IgE at birth or at four months.

Cumulative incidence of eczema

Age (months)	PHF-W (n=53)	CMF (n=53)	Odds ratio	p-value
3	3 (5.7%)	13 (22.8%)	0.20	0.011
6	6 (11.3%)	19 (33.3%)	0.26	0.006
12	7 (13.2%)	21 (36.8%)	0.26	0.004
18	7 (13.2%)	22 (38.6%)	0.24	0.003
24	12 (22.6%)	25 (43.9%)	0.37	0.019
30	15 (28.3%)	25 (43.9%)	0.51	0.090

Cumulative incidence of wheezing

Age (months)	PHF-W (n=53)	CMF (n=53)	Odds ratio	p-value
3	0 (0%)	3 (5.3%)	0.0	0.053
6	2 (3.8%)	3 (5.3%)	0.71	0.494
12	3 (5.7%)	6 (10.5%)	0.51	0.176
18	4 (7.3%)	7 (12.3%)	0.58	0.195
24	5 (9.4%)	9 (15.8%)	0.56	0.125
30	6 (11.3%)	10 (17.5%)	0.60	0.133

Authors' Relevant Conclusions

"Exclusive feeding of hypoallergenic milk formula [PHF-W] in the first 4 months of life has a protective effect in terms of the development of atopic dermatitis in the first 2 years of life, compared to feeding with cow's milk formula."

"In conclusion, exclusive feeding with hypoallergenic formula [PHF-W] in the first 4 months of life among infants with atopic family histories could protect against the development of atopic manifestations, such as eczema, with protection lasting as long as 24 months."

Nestlé Comments

This study focuses on a single intervention of formula (PHF-W vs CMF) in the prevention of atopic disease. The results support both the allergy-prevention effect of PHF-W during the period of active feeding and the long-term beneficial effects of such an intervention, even long after diet diversification.

While the formula intervention had a significant effect on the incidence of eczema, the effect on the incidence of wheezing was not significant. The authors consider that this may be due to the fact that eczema is the most common manifestation of allergy in infants.

While there were no differences in the IgE levels at four months, the authors note that in the PHF-W group there were more infants with an IgE >1UL/ml at birth. The authors see this as an indication that the PHF-W group may have been at greater risk for allergy development, and suggest some effect of the PHF-W on serologic markers.

SUMMARY OF META-ANALYSES, REVIEW PAPERS AND NON-PEER-REVIEWED REPORTS

Meta-analyses

Meta-analytical techniques have been applied to aid in compiling the numerous intervention studies done investigating PHF-W in the primary prevention of allergy. Osborn and Sinn (2003) conducted a meta-analysis of data from allergy-prevention studies involving infant formulas containing any type of hydrolyzed protein. Ram and colleagues (2003) also have published a meta-analysis on infant formula and allergy-prevention, specifically looking at studies that had only respiratory outcomes. The meta-analysis performed by Baumgartner and colleagues (1998) is the most comprehensive attempt at compiling and evaluating the data specifically for PHF-W and allergy-prevention to date. A more detailed narrative description of these publications follows in this section, and a tabular depiction is enclosed as Appendix C-V.

Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

Objective

The objective of this review was to determine whether use of hydrolyzed formulas for infant feeding prevent allergy and food intolerance, what type of hydrolyzed formula (partially or extensively hydrolyzed) is most effective, and which infants would benefit from feeding such a formula.

Inclusion Criteria

- Randomized and quasi-randomized trials comparing the use of a hydrolyzed infant formula to human milk or cow's milk formula
- ≥ 80% follow-up of participants
- Participants within the first 6 months of life without clinical evidence of allergy

Studies Included

Arshad 1992, Hide 1996, 1996
Chan-Yeung 2000
Chandra 1989a, 1991, 1997
Chandra 1989b
Chirico 1997
De Seta 1994
Halken 2000
Juvonen 1994, 1996, 1999
Mallet 1992
Marini 1996
Nentwich 2001
Oldaeus 1997
Saarinen 1999, 2000a, 2000b, 2001
Szajewska 2001
Tsai 1991
Vandenplas 1992, 1995
Vandenplas 1993, Hauser 1993, 1997
Willems 1993

Statistical Analysis

Data were examined for heterogeneity using the chi-square test. The fixed effect model was used for meta-analysis where enrolled infants and interventions were similar and no significant heterogeneity was found. For the comparison of hydrolyzed versus cow's milk formula, an initial analysis was performed including all studies. Subsequent analyses for this comparison were done including only studies with no co-interventions.

Results

Several sub-analyses were performed. The category of 'hydrolyzed formula' refers to studies of both partially and extensively hydrolyzed formulas.

	HF vs CMF	HF vs CMF (no co-intervention)	PHF vs CMF (no co-intervention)	EHF vs PHF (no co-intervention)	HF vs CMF ('good methodology', no co-intervention)
Allergy in infancy	0.65 (0.53-0.81)	0.63 (0.47-0.85)	0.63 (0.47-0.85)	NS	U
Allergy in childhood	0.54 (0.41-0.71)	U	U	U	U
Asthma in infancy	NS	NS	NS	NS	U
Asthma in childhood	NS	U	U	U	U
Eczema in infancy	0.57 (0.44-0.73)	0.48 (0.34-0.66)	0.64 (0.42-0.98)	U	0.46 (0.33-0.66)
Eczema in childhood	0.51 (0.27-0.97)	U	U	U	U
Rhinitis in infancy	0.58 (0.42-0.80)	U	U	NS	U
Rhinitis in childhood	NS	U	U	U	U
Food allergy in infancy	U	U	U	NS	U

Results are listed as typical relative risk, (95% confidence interval). NS = not significant; U = unknown; not reported.

Although the authors intended to do a meta-analysis of data with respect to prolonged feeding of hydrolyzed formula versus human milk feeding and prolonged feeding of hydrolyzed formula versus cow's milk formula (low-risk infants, studies with no co-intervention), no studies belonged to these categories.

Additional results reported in the publication that are not reported here refer to meta-analyses of data regarding the following topics: early short-term feeding of hydrolyzed formula versus human milk feeding (low risk infants); prolonged feeding of extensively hydrolyzed versus cow's milk formula (studies with no co-intervention); prolonged feeding of hydrolyzed versus cow's milk formula (clinical allergy confirmed by test, studies with no co-intervention); early short-term feeding of hydrolyzed formula versus cow's milk formula (no co-intervention); prolonged feeding of hydrolyzed soy formula versus cow's milk formula.

Authors' Relevant Conclusions

"In high risk infants who are unable to be completely breast fed, there is evidence that prolonged feeding with a hydrolysed compared to a cow's milk formula reduces infant and childhood allergy and infant CMA [cow's milk allergy]. "

"Further trials are required to determine if significant clinical benefits persist beyond 5 years of age and if there is any additional benefit from use of an extensive compared to a partially hydrolysed formula."

Ram FSF, Ducharme FM, Scarlett J. Cow's milk protein avoidance and development of childhood wheeze in children with a family history of atopy (Cochrane Review) In: *The Cochrane Library*, Issue 2, 2003. Oxford: Update Software.

Objective

The objective of this review was to quantify the risk of asthma or wheezing in infants fed standard cow's milk based formula compared to infants in whom dietary avoidance of standard cow's milk protein was practiced with either soy-based or hydrolyzed milk formulas (both partially and extensively hydrolyzed formulas were considered). For the purposes of this summary, only information from this review that is relevant to hydrolyzed milk formulas will be discussed.

Inclusion Criteria

- Randomized, controlled studies involving infants fed standard cow's milk protein compared to those in which dietary avoidance of standard cow's milk protein was utilized
- Participants with a family history of at least one first-degree relative
- Intervention of complete or supplemental feeding of hydrolyzed formula for a minimum of the first four months of life compared to regular/standard cow's milk based formula
- Asthma/wheeze as an outcome

Studies Included

Arshad 1992
Chandra 1989a
Mallet 1992
Marini 1996
Tsai 1991
Vandenplas 1992
Zeiger 1989

Statistical Analysis

The comparisons examined included the type of feed used versus standard cow's milk based formula. For dichotomous outcomes, the fixed effect model was used to estimate relative risk. If homogeneity of effect sizes between studies was present, the random effects model was used.

Results

For hydrolyzed formula versus cow's milk formula where dietary restrictions were applied to both the mother and the infant, three studies reporting on period prevalence were included (Arshad 1992, Marini 1996, Zeiger 1989). From 0 to 12 months of age, the relative risk ratio was 0.40 (95% CI of 0.19 – 0.85), in favor of (partially or extensively) hydrolyzed formula. Regarding cumulative incidence for 0 – 12 months, there was a statistically significant difference in favor of hydrolyzed formula for reducing the risk of asthma or wheeze (relative risk ratio of 0.55, 95% CI of 0.31-0.97).

Authors' Relevant Conclusions

"Breast-milk should remain the feed of choice for all babies. In infants with at least one first degree relative with atopy, hydrolyzed formula for a minimum of four months

combined with dietary restrictions and environment measures may reduce the risk of developing asthma or wheeze in the first year or life."

"Our review has shown that in infants at risk of atopic disease, supplementation of breast milk feeding with hydrolyzed milk formula for four months or more in addition to dietary restrictions and house dust-mite reduction, was associated with a lower risk of wheeze in the first 12 months of life compared to standard cow's milk based formula. This protection appeared to persist to two years of age. However, these results should be interpreted with caution, because the number of studies was small and there were a range of other potentially active co-intervention."

Baumgartner M, Brown CA, Exl BM, Secretin MC, van't Hof M, Haschke F. Controlled trials investigating the use of one partially hydrolyzed whey formula for dietary prevention of atopic manifestations until 60 months of age: an overview using meta-analytical techniques. Nutr Res 1998;18:1425-42.

Objective

In an effort to further study the prevention of atopic symptoms in infancy and early childhood, this meta-analysis combined data from studies conducted in infants utilizing one partially hydrolyzed whey protein formula (PHF-W).

Inclusion Criteria

- Prospective, controlled
- Infants at high risk for the development of allergy
- Well-defined feeding groups
- Incorporates Nestlé PHF-W
- Exclusively fed for at least 3 months
- Introduction of solid foods after 3 months of age
- Clear definition of atopic symptoms
- Minimum follow-up period of 3 months
- Data presented as cumulative incidence of atopic manifestations

Studies Included

Chandra 1989a, 1991, 1992, 1997
D'Agata 1996
De Seta 1994
Vassella 1994 (listed as Kraemer in article)
Lam 1992 (unpublished report)
Macagno 1989
Marini 1990
Marini 1996
Martinez Valverde 1993 (thesis; listed as Aljama Garcia in article)
Laforgia 1996 (listed as Mautone in article)
Porch 1998 (abstract cited in article)
Schmidt 1995
Vandenplas 1988
Vandenplas 1992, 1995
Willems 1995

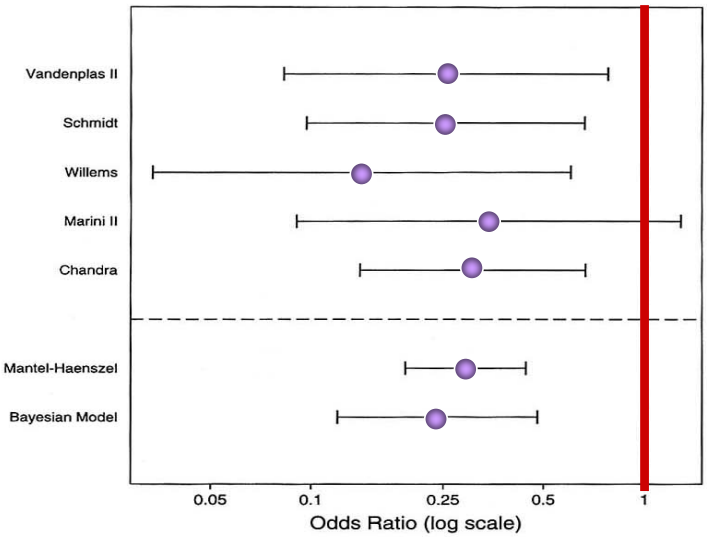
Statistical Analysis

Odds ratios on allergy risk for feeding groups were calculated along with 95% confidence intervals. Two types of meta-analysis techniques were employed: fixed effect model (Mantel-Haenszel) and random effect model (Bayesian).

Results

Comparison of PHF-W with standard cow's milk formula (CMF)-feeding indicates significantly lower odds ratios for the incidence of atopic symptoms in the PHF-W group for all age intervals between 2-6 and 60 months. The 3-6 month data indicate the proportion of infants developing atopic symptoms when fed with PHF-W is about one-fourth the proportion of those fed with CMF (odds ratio = 0.29, 95% CI of 0.18-0.36). The 12-month data indicate an odds ratio of 0.29, CI of 0.19-0.44. The odds ratio between 12-24 and 60 months was significant. The 'number needed to treat' was computed, estimating that feeding three to five **healthy** high risk infants PHF-W rather than CMF will protect one infant from atopic symptoms.

Risk (Odds) of allergic disease by 12 months of age with whey hydrolysates (PHF-W) vs other standard formulas



Authors' Relevant Conclusions

"Breastfeeding or exclusive feeding of a moderately hydrolyzed formula (Nestlé HA formula) for at least three months in infants at high risk for the development of allergic disease, decreases the incidence of atopic manifestations until 60 months of age."

"Comparison of HA- [moderately hydrolyzed whey formula] with CMF [standard cow milk formula]-feeding employing meta-analysis indicates significantly lower odds ratios for the incidence of atopic symptoms in the HA groups for all age intervals between 3-6 and 60 months."

"The number needed to treat calculations estimate that between three and five high risk infants need to receive HA formula in order to protect one infant from atopic symptoms."

"At both 6 and 12 months, the meta-analyses suggest that the proportaion [sic] of infants who develop atopic symptoms in the standard cow milk formula group is about three to four times higher than the proportion in the HA group."

Review Papers

Numerous review papers have been written on potentially appropriate interventions for the primary prevention of allergy. Dietary interventions, targeting both mother and infant, including use of hydrolyzed infant formula, have been discussed as well as environmental actions, such as limiting tobacco and furry pet exposure. In 1995, Halken stated, "Partially hydrolysed formulas (pHF) may be effective in allergy prevention, but due to draw backs of study design and lack of documentations pHF cannot be recommended at present. The results of studies comparing the preventive effect of eHF [extensively hydrolyzed formula] and pHF are awaited." Five years later, in 2000, Zeiger stated, "Both extensively and partially hydrolyzed PHs [protein hydrolysates] compared with cow's milk formula or soy formula have been reported to reduce atopic dermatitis, CMA [cow's milk allergy], and specific cow's milk IgE and even asthma. Outcomes appear similar to exclusive breast-feeding." Some early reviews were skeptical of a role for PHF-W, but as more studies of PHF-W and allergy prevention have been published, with results consistently supporting this association, the role of such a formula in primary prevention has increasingly been acknowledged.

A common thread among the review papers is the call for an adequately powered, multi-center, controlled trial with well-established diagnostic criteria and sufficient follow-up to further substantiate the role of protein hydrolysates in allergy prevention. It is important to note that no review in this area has been written since the 1-year results of the Von Berg study have been published or since the 3-year results of that study have been presented. This study undertaken by the German government addresses the majority of concerns expressed by the authors of the review in the conduct of a large, multi-center trial in this area. Future review papers written taking the Von Berg study into consideration may state PHF-W's role in the primary prevention of allergy more strongly.

Summary tables of the meta-analyses and quotations from selected review papers are located in Appendix C-V.

Non-Peer-Reviewed Reports

To address any potential for publication bias, non-peer-reviewed sources were also examined for all relevant studies, and these were also included among the supportive evidence. Thus, in addition to the many peer-reviewed publications of allergy-prevention studies discussed above, three abstracts (Barberi 1993, Chandra 1992, Lam 1992), two doctoral theses (Silva Rey 1996 and Martinez Valverde 1993), two reports published in the Nestlé Nutrition Workshop series (Schmidt 1995 and Iikura 1995), and one letter to the editor (Vandenplas 1992) are referenced in this petition.

In the case of two of these reports, this petition includes peer-reviewed, published studies on the same population cohort. The Chandra abstract is the presentation of the 3-year data on a cohort that is reported on in several peer-reviewed publications (Chandra 1989, 1991, 1997). Similarly, the Vandenplas Letter to the Editor is a commentary on the 3-year

data of a cohort that is reported on in two separate peer-reviewed publications (Vandenplas 1992, 1995).

Two of the abstracts (Barberi 1993, Lam 1992) have been published only in abstract form and report on studies of infant cohorts that do not appear in the peer-reviewed literature.

Data from the study conducted by Lam (1992) were presented in abstract form at the 6th Annual Scientific Meeting of Hong Kong College of Physicians and Hong Kong College of Paediatricians. Additional data was provided in an internal report to Nestlé (Nestec SA) during that same year. The Lam data are also presented in the Baumgartner meta-analysis (1998). The Barberi and Lam abstracts are included in the Summary Table at Appendix C-III, which covers all non-peer-reviewed reports that met search criteria by reporting on the use of 100% whey partially hydrolyzed formula for the prevention of allergic diseases in infants when compared to standard intact cow's milk formula.

Overall, the results reported in these non-peer-reviewed studies are completely consistent with those published in peer-reviewed journals. For those reports where cumulative incidences and odds risk ratios were possible to calculate, PHF-W reduced the risk of allergy with varying degrees of statistical significance, when compared to CMF. Similarly also, no study reported, with or without statistical significance, an increase in allergy incidence.

APPENDICES

Appendix C-I: Economic Implications

Given the public health implications of a cost-effective strategy for primary prevention, the economic impact has been explored in some publications.

Chandra (1997) discusses the economic implications of the use of PHF-W as an allergy prevention strategy. According to Chandra, the average estimated cost of treatment of all high-risk children with allergic disease in Newfoundland until the age of five years is about $740,000 per year. Exclusive breastfeeding would be the most cost-effective prevention strategy. However, in children who are not breastfed, feeding PHF-W would be expected to lower the total cost of treatment to $400,000 per year. According to Chandra, extensively hydrolyzed formulas would perform similarly, but the prohibitive cost of such formulas (3 to 4 times more than standard CMF) makes it an economically impractical recommendation for allergy prevention in the general population. In comparison, PHF-W adds no incremental cost over standard CMF.

The cost of lifetime care for a person with cow's milk allergy in childhood has been estimated at $3,117, with 72% of that amount attributed to direct costs and the remainder resulting from lost workdays of parents (Zeiger 1998).

Allergic disease is a growing public health issue. As atopic manifestations in infancy often lead to atopic manifestations in children and adults, cost-effective and practical primary prevention strategies are valuable public health measures to reduce the economic and social burden of persons affected by this disease. Breastfeeding is the most cost-effective approach, but for those healthy infants who require supplementation with infant formula, PHF-W is the most logical option for the primary prevention of allergy with no additional cost over that of conventional cow's milk formulas.

Appendix C-II: Prospective, peer-reviewed, published studies comparing PHF-W to intact cow's milk protein for allergy prevention

The following table includes all studies* evaluating the use of PHF-W for the prevention of allergic diseases in infancy when compared to CMF.

- 19 peer-reviewed, published reports of studies of 13 population cohorts are identified and included
- Does not include partial casein-whey hydrolysates**

The table includes:

- Name of the first author and year of publication
- Design Type and Quality Factor (as defined by FDA)
- Total sample size of the population cohort
- Randomization and blinding (as reported by the authors, although neither breastfeeding nor studies of EHF can in practice be double-blinded)
- Whether the study involved exclusive formula feeding (Formula) or allowed for supplementation of formula with breastfeeding (Formula +/- BF) and sample size of each group
- Any feeding restrictions on these groups
- Outcomes studied
- Methodology of diagnosis
- Results as related specifically to the allergy preventive effect of the study formula

*All studies were identified which compared the use of a partially hydrolyzed whey protein formula and an intact cow's milk protein formula, and compared their efficacy for the purposes of prevention of any allergic manifestation.

**A study by Oldaeus and colleagues (1997) utilizes a partial hydrolysate that is 60:40 whey:casein manufactured for the study by Mead Johnson; a study of premature infants by Szajewska and colleagues (2004) utilizes a partial hydrolysate that is 60:40 whey:casein manufactured by Nutricia; a study by Han and colleagues (2003) utilizes a partial hydrolysate that is whey and casein manufactured by Maeil Dairy Industry.

Abbreviations used:

B = blinded
BF = breastfed
BM = breast milk
CMF = cow's milk formula
CMP = cow's milk protein
DB = double-blind
DBPCFC = double-blind placebo-controlled food challenge
EHF-C = extensively hydrolyzed formula-casein
EHF-W = extensively hydrolyzed formula-whey
FC = food challenge
GI = gastrointestinal
PHF-W = partially hydrolyzed formula-whey
R = randomized
RAST = radioallergosorbent tests
SB = single-blind
SPT = skin prick test
U = unknown

Prospective, peer-reviewed, published studies comparing PHF-W‡ to intact cow's milk protein for allergy prevention

Report	Design Type	Quality Factor	Population Cohort	R	B	Feeding groups[+]	Feeding restrictions	Outcome measures	Diagnosis	Results
Becker 2004, Chan-Yeung 2000	1	+	545 infants with at least 1 first-degree relative with asthma or 2 first-degree relatives with other IgE-mediated allergic diseases	Y	SB	BF encouraged in both intervention and control groups; Control = usual care which could include CMF (8.3% received PHF-W) (n=242); Intervention = BF +/-PHF-W + avoidance of dust mite, pet allergens, tobacco smoke (n=251)	Intervention: for last trimester of pregnancy and lactation, moms excluded nuts, seafood; No solid food for 6 mo; Infants excluded CM, seafood, peanuts for 1 yr Control: usual care	Asthma Recurrent wheeze Rhinitis without cold	Exam SPT	Chan-Yeung 2000: At 12 mo, risk for rhinitis without colds and possible or probable asthma were significantly reduced in intervention group. Becker 2004: At 24 mo, significantly fewer children had asthma in the intervention group compared with control. No significant difference for atopy between the intervention and control groups.
Von Berg 2003†	1	+	2252 infants with first degree relative with an allergic disease	Y*	DB	PHF-W+/-BF (n=241) EHF-C+/-BF (n=210) EHF-W+/-BF (n=238) CMF+/-BF (n=256)	Formula provided for first 6 mo, no solid foods during first 4 mo; thereafter no more than 1 new food/week	Atopic dermatitis Food allergy manifestation in GI tract Urticaria	Exam For uncertain reactions, DBPCFC	At 12 mo, incidence of allergic manifestation was significantly reduced by using EHF-C compared with CMF, and the incidence of atopic dermatitis was significantly reduced by using EHF-C and PHF-W.
Chan 2002	1	+	153 infants with first degree relative with atopy	Y	SB	PHF-W (n=53) CMF (n=57)	Formulas fed exclusively for 4 mo, unrestricted weaning diet	Eczema Urticaria Wheezing	Exam IgE	Cumulative occurrence of eczema significantly lower in PHF-W at 3,6,12, & 24 months, not significant at 30 mo. No difference in cord or serum IgE levels between groups.
Exl 1998, 2000	3	∅	1130 infants recruited from all births (allergy risk was not inclusion criteria)	N	N	BF+/-PHF-W (n=466) BF+/-CMF (n=535)	BF + PHF-W exclusive for 4mo, BF + CMF no restrictions	GI symptoms Lower respiratory findings Skin findings Upper respiratory findings	Exam	At 6 mo, cumulative symptoms were significantly lower in the BF +/-PHF-W group, mainly due to differences in skin parameters.

* Mothers were encouraged to breast-feed; those who chose not to breast-feed were randomized to the formula groups studied.
‡ With the exception of Chirico 1997, PHF-W refers to Nestlé's PHF-W product. In Chirico 1997, PHF-W refers to Vivena HA-Primigiorni HA, Plada, Milan, Italy.
[+] With the exception of D'Agata 1996 and De Seta 1994, n's listed here are based on those who completed the study at 12 months (or if no 12 month time-point, at the end of the study) in the indicated group, not on the number of subjects randomized to each group.
[δ] These results are from non-peer reviewed publications.

Prospective, peer-reviewed, published studies comparing PHF-W‡ to intact cow's milk protein for allergy prevention (continued)

Report	Design Type	Quality Factor	Population Cohort	R	B	Feeding groups[+]	Feeding restrictions	Outcome measures	Diagnosis	Results
Chandra 1989, 1991, 1992[δ], 1997	1	+	288 infants with first degree relative with atopy	Y*	DB	PHF-W (n=68) CMF (n=67) Soy (n=68) BF (n=60)	Mom's diet unrestricted; Exclusive for 6mo	Asthma Colic Eczema GI symptoms Otitis Rhinitis	DBPCFC Exam SPT	1989: At 6mo, PHF-W had significantly fewer manifestations of possible allergic etiology compared to all other groups (including BF). 1991: At 12 and 18 mo, cumulative incidence of atopic symptoms was significantly lower in the PHF-W group as compared to CMF and soy. There was no difference between PHF-W and BF. 1992[δ]: At the end of 3 yr, the number of infants having one or more symptoms and signs of allergy was significantly lower in the PHF-W group as compared to CMF and soy. 1997: At 5 years, the incidence in allergic disease in PHF-W was significantly lower than CMF. Differences in allergic manifestations between PHF-W and BF were not significant. Occurrence of both eczema and asthma was lower in BF and PHF-W as compared to CMF and soy. DBPCFC showed a lower prevalence of food allergy in PHF-W compared with other formulas.
Chirico 1997	1	+	51 at-risk infants with atopic mother 23 control infants with no atopic history	Y*	U	At-risk: PHF-W‡ (n=21) CMF (n=14) BF (n=16) Control: CMF (n=13) BF (n=10)	Exclusive formula or BM for 6 mo At-risk: maternal dietary restrictions if BF, delayed weaning, avoidance of smoking, nurseries, reduction of pet and mite exposure Control: delayed weaning, avoidance of smoking	Eczema	Exam RAST Specific IgE, IgG, IgG4 Total IgE	At 6 mo, 4/16 at-risk BF and 2/14 at-risk CMF had eczema. RAST was positive for milk or egg proteins in 5/16 at-risk BF, 1/21 at-risk PHF-W‡, 1/14 at-risk CMF, 2/10 BF control, 3/13 CMF control. At-risk PHF-W‡ had significantly lower total IgE than at-risk CMF and control CMF. At-risk PHF-W‡ had significantly lower IgG and IgG4 compared to at-risk CMF and similar values to BF.

* Mothers were encouraged to breast-feed; those who chose not to breast-feed were randomized to the formula groups studied.
‡ With the exception of Chirico 1997, PHF-W refers to Nestlé's PHF-W product. In Chirico 1997, PHF-W refers to Vivena HA-Primigiorni HA, Plada, Milan, Italy.
[+] With the exception of D'Agata 1996 and De Seta 1994, n's listed here are based on those who completed the study at 12 months (or if no 12 month time-point, at the end of the study) in the indicated group, not on the number of subjects randomized to each group.
[δ] These results are from non-peer reviewed publications.

Prospective, peer-reviewed, published studies comparing PHF-W‡ to intact cow's milk protein for allergy prevention (continued)

Report	Design Type	Quality Factor	Population Cohort	R	B	Feeding groups[+]	Feeding restrictions	Outcome measures	Diagnosis	Results
D'Agata 1996	3	∅	125 infants with first degree relative with atopy	U	U	PHF-W (n=50) CMF (n=15) Soy (n=30) BF (n=30)	BF: exclusive feeding for 6 mo with maternal dietary restrictions; Formula: exclusive feeding for 4-5 mo	Asthma Eczema GI symptoms Rhinitis Urticaria	IgE RAST SPT	At 4 years, BF and PHF-W had lower incidence of atopic manifestations than Soy and CMF. From birth to 12 mo, IgE levels were lower in BF and PHF-W than CMF and Soy.
Marini 1996	1	+	359 infants with biparental atopy	Y*	SB	Parents self-selected to Intervention (dietary and environmental). Intervention: PHF-W+/-BF (n=71) CMF+/-BF (n=64) BF (n=108) Non-intervention: CMF+/-BF (n=35) BF (n=33)	Intervention: BM or formula exclusive 5 mo, mom's diet restricted (low CMP), hypoantigenic weaning diet Non-intervention: unrestricted	Dermatitis GI symptoms Rhinitis Urticaria Wheezing	Exam IgE Open FC RAST SPT	At 1 and 2 years, there was a lower incidence of all allergic symptoms in the intervention group. Within the intervention group, those fed CMF had significantly more allergies than BF and PHF-W.
Vandenplas 1992a, 1992b[δ], 1995	1	+	75 infants with 2 first degree relatives with atopy	Y	DB	PHF-W (n=32) CMF (n=35)	Exclusive formula fed to 4 mo, then added grated apple, unrestricted diet after 6 mo.	Angioedema Asthma Atopic dermatitis Chronic rhinitis Chronic cough GI symptoms Urticaria	Exam IgE Open FC RAST SPT	1992a: Incidence of atopic disease was reduced up to the age of 12 months in the PHF-W group. 1992b[δ]: PHF-W exhibited significantly fewer atopic features compared to CMF, to the age of 3 years. This difference was due to decreased incidence of atopy during the first 6 months of life. 1995: At 6 and 12 mo, the prevalence of symptoms suggestive for atopy was significantly lower in PHF-W. Between 1 and 3 years, the cumulative number of manifestations suggestive of atopic diseases was significantly lower in PHF-W. Between 3 and 5 years, there was no difference in the number or severity of atopic manifestations. There was no difference between groups if only new cases after 6 mo were considered.

* Mothers were encouraged to breast-feed; those who chose not to breast-feed were randomized to the formula groups studied.
‡ With the exception of Chirico 1997, PHF-W refers to Nestlé's PHF-W product. In Chirico 1997, PHF-W refers to Vivena HA-Primigiorni HA, Plada, Milan, Italy.
[+] With the exception of D'Agata 1996 and De Seta 1994, n's listed here are based on those who completed the study at 12 months (or if no 12 month time-point, at the end of the study) in the indicated group, not on the number of subjects randomized to each group.
[δ] These results are from non-peer reviewed publications.

Prospective, peer-reviewed, published studies comparing PHF-W‡ to intact cow's milk protein for allergy prevention (continued)

Report	Design Type	Quality Factor	Population Cohort	R	B	Feeding groups[+]	Feeding restrictions	Outcome measures	Diagnosis	Results
De Seta 1994	1	∅	108 infants with first degree relative with allergy	Y*	U	PHF-W (n=23) CMF (n=39) BF (n=46)	Exclusive formula for 6 mo	Asthma CMP intolerance with GI manifestations Eczema	Exam	Use of PHF-W as compared to intact CMF resulted in a non-significant reduction in incidence of allergic diseases at 6 and 24 mo.
Willems 1993	3	∅	175 infants with high cord IgE &/or family history of atopy	N	N	PHF-W (n=30) CMF (n=37)	Exclusive formula for 3 mo	Asthma Bronchitis Eczema GI symptoms Rhinitis Sleeping difficulties	Exam	Only 67 (30 PHF-W, 37 CMF) infants followed protocol. At 3 ($p<0.07$) & 12 mo ($p<0.007$), cumulative allergic symptoms were lower in PHF-W group that followed protocol compared to all other subjects (including those in PHF-W that did not follow protocol).
Tsai 1991	1	∅	33 infants with family allergy score >3	Y	U	PHF-W + BF (n=15) CMF (n=18)	PHF-W+BF group had BM for first 1-2 mo followed by PHF-W until 6 mo; 2 infants in this group were exclusively BF	Atopic dermatitis Allergic rhinitis Wheezing	Exam IgE	After 12 mo, infants in CMF group had a non-significant higher incidence of moderate-severe atopic dermatitis and allergic rhinitis. No difference in the incidence of wheezing.
Vandenplas 1988, 1989	3	∅	75 infants with first degree relative with atopic disease	N	N	PHF-W (n=15) PHF-W then CMF (n=11) CMF (n=14) CMF then PHF-W (n=13) BF (n=9)	Exclusive for 4 mo; for combination groups, formulas given for 2 mo each	GI symptoms Respiratory tract symptoms Skin symptoms	Exam IgE RAST SPT	After 4 mo, none of the infants in PHF-W developed symptoms of atopy; SPT was negative. In PHF-W then CMF group, 6 infants had allergic manifestation that disappeared on PHF-W, reappearing on CMF. In CMF then PHF-W group, 4 infants developed allergic manifestations. 1 infant in BF group had eczema. In CMF group, 8 infants had atopic symptoms before the age of 4 mo.

* Mothers were encouraged to breast-feed; those who chose not to breast-feed were randomized to the formula groups studied.
‡ With the exception of Chirico 1997, PHF-W refers to Nestlé's PHF-W product. In Chirico 1997, PHF-W refers to Vivena HA-Primigiorni HA, Plada, Milan, Italy.
[+] With the exception of D'Agata 1996 and De Seta 1994, n's listed here are based on those who completed the study at 12 months (or if no 12 month time-point, at the end of the study) in the indicated group, not on the number of subjects randomized to each group.
[δ] These results are from non-peer reviewed publications.

References:

Becker A, Watson W, Ferguson A, Dimich-Ward H, Chan-Yeung M. The Canadian asthma primary prevention study: outcomes at 2 years of age. J Allergy Clin Immunol 2004;113:650-6.

Chan YH, Shek LPC, Aw M, Quak SH, Lee BW. Use of hypoallergenic formula in the prevention of atopic disease among Asian children. J Paediatr Child Health 2002;38:84-88.

Chan-Yeung M, Manfreda J, Dimich-Ward H, Ferguson A, Watson W, Becker A. A randomized controlled study on the effectiveness of a multifaceted intervention program in the primary prevention of asthma in high-risk infants. Arch Pediatr Adolesc Med 2000;154:657-63.

Chandra RK, Singh G, Shridhara B. Effect of feeding whey hydrolysate, soy and conventional cow milk formulas on incidence of atopic disease in high risk infants. Ann Allergy 1989;63:102-6.

Chandra RK, Hamed A. Cumulative incidence of atopic disorders in high risk infants fed whey hydrolysate, soy, and conventional cow milk formulas. Ann Allergy 1991;67:129-32.

Chandra RK, Hamed A, Prasad C, Singh GK. Cumulative incidence of allergic disorders in high risk infants fed whey hydrolysate, soy and conventional cow's milk formulas. Am J Clin Nutr 1992;56:758. (Abstract)

Chandra, RK. Five-year follow-up of high-risk infants with family history of allergy who were exclusively breast-fed or fed partial whey hydrolysate, soy, and conventional cow's milk formulas. J Pediatr Gastroenterol Nutr 1997;24:380-8.

Chirico G, Gasparoni A, Ciardelli L, De Amici M, Colombo A, Rondini G. Immunogenicity and antigenicity of a partially hydrolyzed cow's milk infant formula. Allergy 1997;52:82-8.

D'Agata A, Betta P, Sciacca P, Morano C, Practico G, Curreri R, Quattrocchi O, Sciacca F. The role of preventing diet in newborn at risk of atopy. Follow-up results. Med Surg Ped 1996;18:469-72.

De Seta L, Siani P, Cirillo G, Di Gruttola M, Cimaduomo L, Coletta S. Prevention of allergic disease by an hypoallergenic formula: preliminary results at the 24 months follow-up. Med Surg Ped 1994;16:251-4.

Exl BM, Deland U, Wall M, Preysch U, Secretin MC, Shmerling DH. Zug-Frauenfeld nutritional survey ("Zuff Study"): allergen-reduced nutrition in a normal infant population and its health –related effects: results at the age of six months. Nutr Res 1998;18:1443-62.

Exl BM, Deland U, Secretin MC, Preysch U, Wall M, Shmerling DH. Improved general health status in an unselected infant population following an allergen-reduced dietary intervention programme: the ZUFF-STUDY-PROGRAMME. Part II: infant growth and health status to age 6 months. Eur J Nutr 2000;39:145-56.

Marini A, Agosti M, Motta G, Mosca F. Effects of a dietary and environmental prevention programme on the incidence of allergic symptoms in high atopic risk infants: three years follow-up. Acta Paediatr Suppl 1996;414:1-22.

Tsai Y, Chou C, Hsieh K. The effect of hypoallergenic formula on the occurrence of allergic diseases in high risk infants. Acta Paed Sin 1991;32:137-44.

Willems R, Duchateau J, Magrez P, Denis R, Casimir G. Influence of hypoallergenic milk formula on the incidence of early allergic manifestations in infants predisposed to atopic diseases. Ann Allergy 1993;71:147-50.

Vandenplas Y, Deneyer M, Sacre L, Loeb H. Preliminary data on a field study with a new hypo-allergenic formula. Eur J Pediatr 1988;148:274-7.

Vandenplas Y, Malfroot A, Dab I. Short-term prevention of cow's milk protein allergy in infants. Immunology & Allergy Practice 1989;11:430-7.

Vandenplas Y, Hauser B, Van den Borre C, Sacre L, Dab I. Effect of a whey hydrolysate prophylaxis of atopic disease. Ann Allergy 1992;68:419-24.

Vandenplas Y. Atopy at 3 years in high-risk infants fed whey hydrolysate or conventional formula. Lancet 1992;339:1118 (Letter to the Editor)

Vandenplas Y, Hauser B, Van den Borre C, Clybouw C, Mahler T, Hachimi-Idrissi S, Deraeve L, Malfroot A, Dab I. The long-term effect of a partial whey hydrolysate formula on the prophylaxis of atopic disease. Eur J Pediatr 1995;154:488-94.

Von Berg A, Koletzko S, Grübl A, Filipiak-Pittroff B, Wichmann H, Bauer CP, Reinhardt D, Berdel D, German Infant Nutritional-Intervention Study Group. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. J Allergy Clin Immunol 2003;111:533-40.

Appendix C-III: Non-peer-reviewed studies comparing PHF-W to intact cow's milk protein for allergy prevention

The following table includes non-peer reviewed abstracts and presentations reporting the use of PHF-W for the prevention of allergic diseases in infancy when compared to CMF.

- 6 reports of studies of 6 population cohorts are identified and included

The table includes:

- Name of the primary investigator and year of report
- Design Type and Quality Factor (as defined by FDA)
- Total sample size of the population cohort
- Randomization and blinding (as reported by the authors, although neither breastfeeding nor studies of EHF can in practice be double-blinded)
- Whether the study involved exclusive formula feeding (Formula) or allowed for supplementation of formula with breastfeeding (Formula +/- BF) and sample size of each group
- Any feeding restrictions on these groups
- Outcomes studied
- Methodology of diagnosis
- Results as related specifically to the allergy preventive effect of the study formula

Abbreviations used:

B = blinded
BF = breastfed
CM = cow's milk
CMA = cow's milk allergy
CMF = cow's milk formula
DB = double-blind
GI = gastrointestinal
PHF-W = partially hydrolyzed formula-whey
R = randomized
RAST = radioallergosorbent tests
SB = single-blind
SPT = skin prick test
U = unknown

Summary Table - Non-peer-reviewed publications of studies comparing PHF-W‡ to intact cow's milk protein for allergy prevention

Report	Design Type	Quality Factor	Population Cohort	R	B	Feeding groups[+]	Feeding restrictions	Outcome measures	Diagnosis	Results
Silva Rey 1996 (thesis)	1	+	152 infants with first degree relative with allergic disease	Y*	SB	BF<1 mo+CMF (n=42) BF<1mo+PHF-W (n=20) BF>4mo+CMF (n=35) BF>4mo+PHF-W (n=47)	Introduction of egg at 12 mo, fish at 18 mo, dried fruit at 24 mo	Atopic dermatitis Food allergy/intolerance Recurrent wheezing	Exam IgE SPT	At 6 and 12 mo, frequency of atopic manifestations was significantly lower in breastfed and/or PHF-W groups than CMF ($p<0.005$). At 6 and 12 mo, incidence of atopic dermatitis was significantly less in PHF-W than other groups. No differences were seen at 24 mo.
Iikura 1995	1	∅	126 infants from general population	Y*	N	PHF-W+BF (n=33) CMF+BF (n=59) BF (n=27)	Solid food intake started after 5 mo	Respiratory Skin	Exam IgE	50/126 (40%) infants had no family history of atopy. At 4 mo and 1 year, PHF-W+BF had significantly fewer allergic symptoms than CMF+BF.
Schmidt 1995	3	∅	1370 infants with first degree relative with allergy	N	SB	PHF-W+/-BF (n=206) CMF+/-BF (n=166) BF +/- restrictions (n=247)	No weaning foods up to 5th mo. No restrictions in any group after 6th month	Asthma Atopic eczema CMA Pollen allergy	Exam Parent records of symptoms RAST	At 12 mo, the cumulative prevalence of atopic disease was significantly lower in the group fed PHF-W as compared to the CMF group.
Lam 1992 (abstract and internal report)	1	+	120 infants with family history of allergy	Y*	DB	PHF-W (n=50) CMF (n=50) BF (n=20)	Exclusive formula or BF for 6 mo	Colic Eczema Respiratory atopy Urticaria	Exam IgE RAST SPT	At 6 mo, the incidence of atopic manifestations was significantly lower in PHF-W and BF groups than CMF. There was no difference in eczema incidence among the 3 groups.
Martinez Valverde 1993 (thesis)	1	∅	150 infants with first degree relative with atopic illness	Y*	N	PHF-W (n=50) CMF (n=50) BF+/- restrictions (n=50)	BF +restrictions mothers: no dairy	GI Respiratory Skin	Not stated	After 3 months, the greatest allergy prevention benefit was seen in BF+ restrictions followed by PHF-W.
Barberi 1993 (presentation)	1	∅	815 infants with atopic risk	Y*	U	PHF-W (n=103) CMF (n=84) Soy (n=37) BF	BF mothers: limited CM and eggs	Diarrhea Eczema Vomiting Wheezing	Exam	At 360 d, allergic pathology was clinically evaluated in 15.53% of PHF-W, 32.4% CMF, and 58.3% soy.

Formatted: French (France)

* Mothers were encouraged to breast-feed; those who chose not to breast-feed were randomized to the formula groups studied.

[+] N's listed here are based on those who completed the study at 12 months (or if no 12 month time-point, at the end of the study) in the indicated group, not on the number of subjects randomized to each group.

‡ Throughout this table, PHF-W refers to Nestlé's PHF-W product.

References:

Barberi I, Salpietro DC, Catalioto G, Fulia F. Clinical trial of a new hypoallergenic formula in risk infants. 2nd World Congress of Perinatal Medicine, Rome and Florence 1993 (September).

Iikura Y, Akimoto K, Ebisawa M, Onda T, Akazawa A, Saito H, Kimura T, Ishizawa K, Koya N. Effect of hydrolyzed whey protein formula for babies on development of allergic symptoms during infancy. Nestlé Nutrition Workshop Intestinal Immunology and Food Allergy, Raven Press 1995;34:269-75.

Lam BCC, Yeung CY. The effect of breast milk, infant formula and hypoallergenic formula on incidence of atopic manifestation in high risk infants. 6th Annual Scientific Meeting of Hong Kong College of Physicians and Hong Kong College of Paediatricians, Hong Kong 1992 (October).

Lam BCC, Yeung CY. The effect of breast milk, infant formula and hypoallergenic formula on incidence of atopic manifestation. Internal report, Nestec SA 1992.

Martinez Valverde A. Study on the assessment of serum IgE and specific IgE to Alpha lactalbumin, Beta lactoglobulin, and casein in infants fed hypoallergenic formula and other forms of feeding. Thesis, Universidad de Malaga, Spain, 1993.

Schmidt E, Eden-Köhler J, Tonkaboni F, Tölle J. Alimentary allergy prevention in infants with familial increased allergic risk: the effect of different feeding regimens in the first 6 months on atopic manifestations during the first year of life. A large-scale feeding trial. Nestlé Nutrition Workshop Intestinal Immunology and Food Allergy, Raven Press 1995;34:231-49.

Silva Rey AL, Garcia G, Nogales A. Preventive effect of a partially hydrolysed cow milk infant formula: clinical and biological 24 month follow-up study. Thesis, Spain, 1996.

Appendix C-IV: Overview graphs of cumulative incidence and odds ratios of allergic manifestations and atopic dermatitis

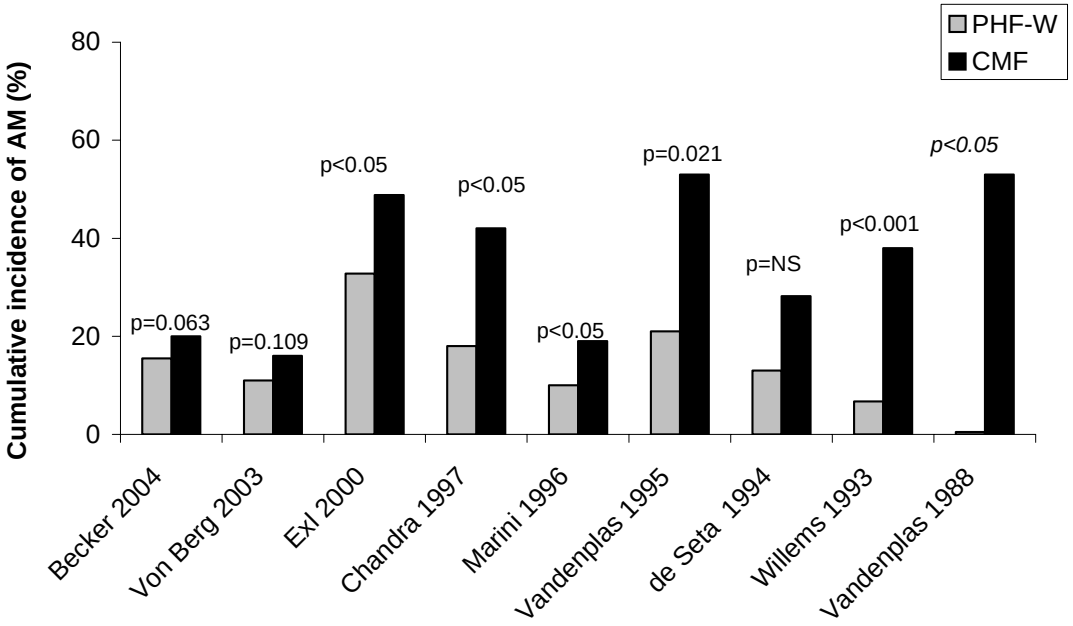
The following graphs depict the cumulative incidence of allergic manifestations (AM) and atopic dermatitis (AD) for Nestlé PHF-W studies of primary prevention of allergic disease in infancy.

For all graphs:

- Values are those listed in both prospective, peer-reviewed and non-peer reviewed reports.
- Values are those comparing the use of Nestlé PHF-W versus intact CMF, whether the study may or may not have included other formulas or a breastfed group, and whether or not the study may have required exclusive formula-feeding or allowed for supplementation of study formula with breastfeeding.
- Values are those reported for studies following infants up to 12 months of age. If 12 month data were not available, the closest time point data were collected at <12 months were used.
- Separate values for AM and AD are shown for the same study if they are reported or if data were available for calculation.
- Not all studies reported both AM and AD.
- With the exception of Becker 2004, AD is included as an AM in the reports and calculations for all studies.
- When available, p-values are listed as reported by the authors. If a p-value is in italics, this indicates the p-value is based on odds ratios (OR) and confidence intervals (CI) calculated, (See 'Calculation of Odds Ratios and 95% Confidence Intervals', page 41.)

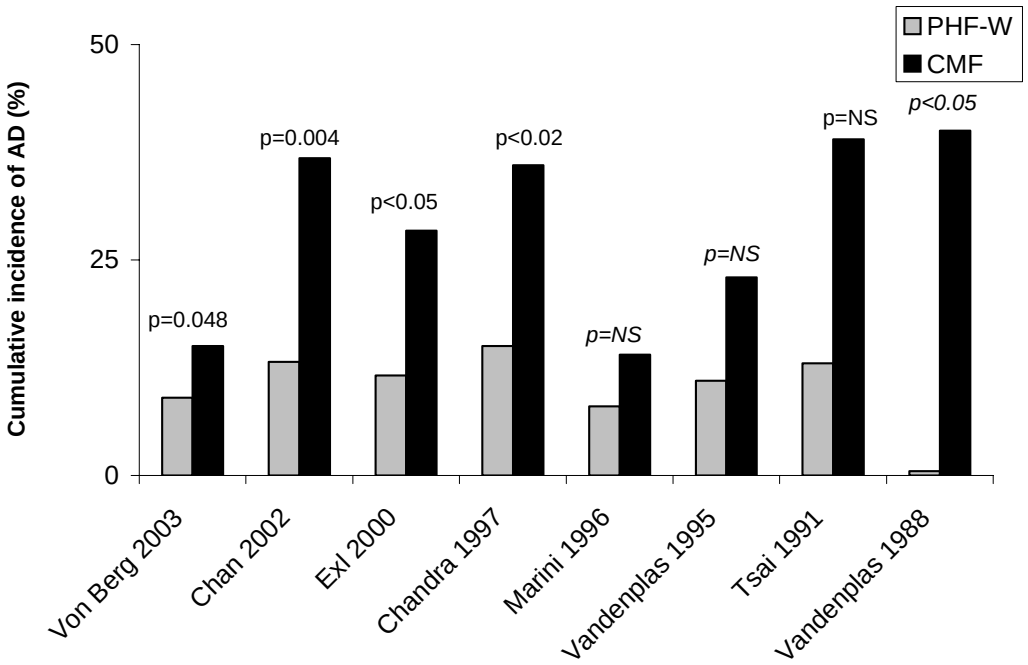
*Because the figures only depict cumulative incidence for studies up to 12 months of age, the D'Agata 1996 study is not shown as outcomes were measured only at 4 years of age.

Cumulative Incidence of Allergic Manifestations in Studies up to 12 mo of Age: PHF-W vs CMF (Peer-Reviewed)



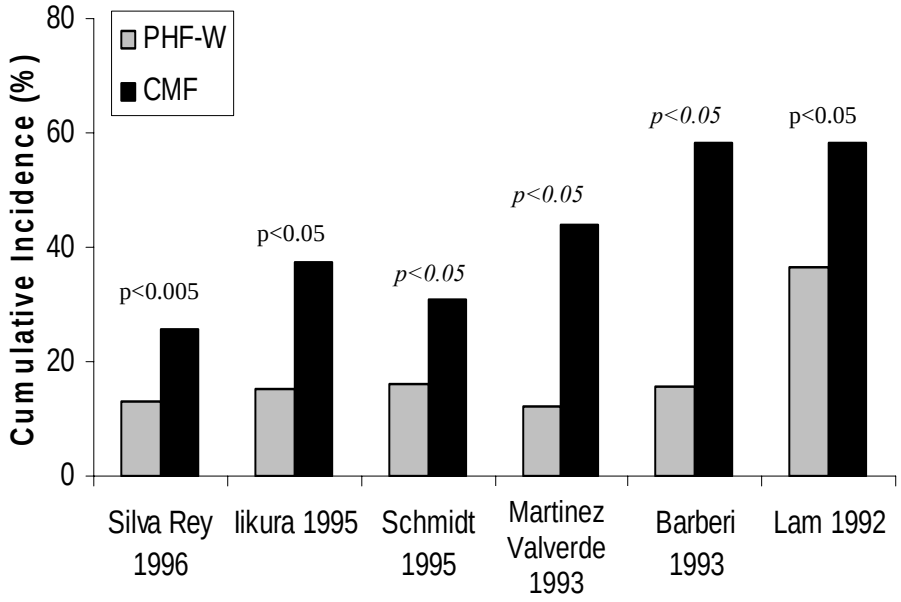
- *Graph depicts only published, peer-reviewed, prospective trials with data collection at timepoints ≤12 months.*
- *For all studies except Becker 2004, AM includes AD as one of the allergic outcomes assessed; for Becker 2004, AM refers to asthma alone.*
- *4 months: Vandenplas 1988 (reported as "dermatological symptoms"); 6 months: Exl 2000 (reported as "skin symptoms"); De Seta 1994; 12 months: Becker 2004, Von Berg 2003, Chandra 1997, Marini 1996, Vandenplas 1995, Willems 1993*
- *p-values in italics indicate that no p-value is reported in publication; p-value is based on calculated OR and 95% CI*
- *p-value for Marini 1996 is published as p<0.05; however, the calculated 95% CI indicates the upper limit of the CI is >1.0*

Cumulative Incidence of Atopic Dermatitis in Studies up to 12 mo of Age: PHF-W vs CMF (Peer-Reviewed)



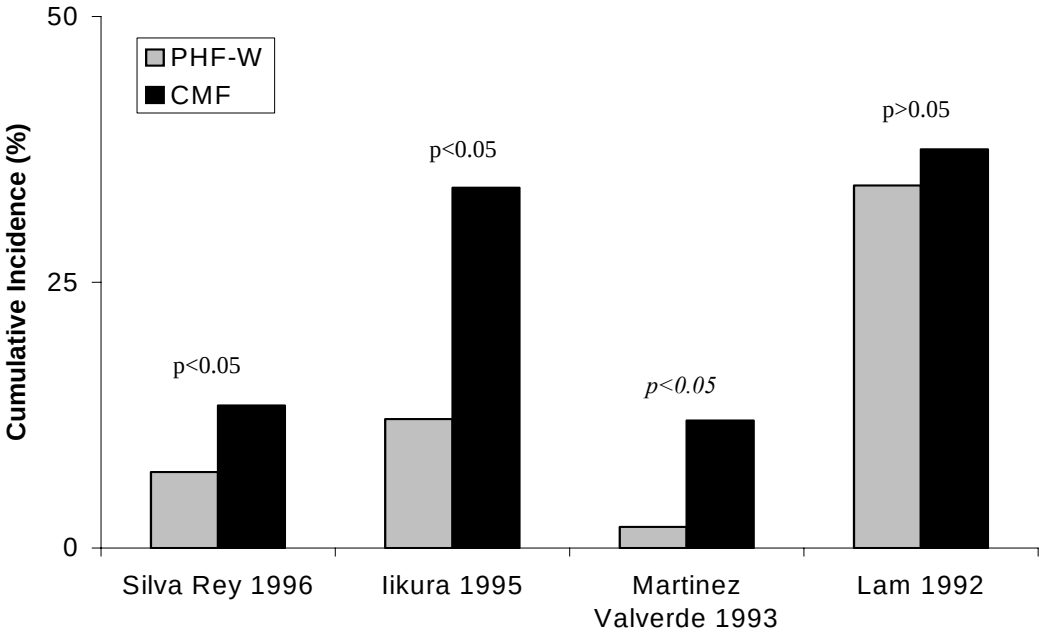
- *Graph depicts only published, peer-reviewed, prospective trials with data collection at timepoints ≤12 months.*
- *4 months: Vandenplas 1988 (reported as "dermatological symptoms"); 6 months: Exl 2000 (reported as "skin symptoms"); 12 months: Von Berg 2003, Chan 2002, Chandra 1997, Marini 1996, Vandenplas 1995, Tsai 1991*
- *p-values in italics indicate that no p-value is reported in publication; p-value is based on calculated OR and CI*

Cumulative Incidence of Allergic Manifestations in Studies up to 12 mo of Age: PHF-W vs CMF (Non-Peer-Reviewed)



- *3 mo: Martinez Valverde (high-risk infants only); 6 mo: Lam, 12 mo: Silva Rey, Iikura, Schmidt, Barberi*
- *Iikura 1995 in general population*
- *p-values in italics indicate that no p-value is reported in publication; italicized p-values are based on calculated OR and 95% CI*

Cumulative Incidence of Atopic Dermatitis in Studies up to 12 mo of Age: PHF-W vs CMF (Non-Peer-Reviewed)



- *3 mo: Martinez Valverde (high-risk infants only); 6 mo: Lam, 12 mo: Silva Rey, Iikura*
- *Iikura 1995 in general population*
- *p-values in italics indicate that no p-value is reported in publication; italicized p-values are based on calculated OR and 95% CI*

The following figures refer to studies of allergic manifestations (AM) and atopic dermatitis (AD) for both peer-reviewed, published and non-peer reviewed Nestlé PHF-W versus CMF studies of primary prevention of allergic disease in infancy.

- Values are those listed in the reports or are calculated from data reported in these studies using the method stated on the following page.
- Values are those for the odds ratio (OR) and 95% confidence intervals (CI) of developing AM or AD when using PHF-W versus intact CMF, whether the study may or may not have included other formulas or a breastfed group, and whether or not the study may have required exclusive formula-feeding or allowed for supplementation of study formula with breastfeeding.
- Values are those reported for studies following infants up to 12 months of age*. If 12 month data were not available, the closest time point data were collected at <12 months were used.
- Separate values for AM and AD are shown for the same study if they are reported or if data were available for calculation.
- Not all studies reported both AM and AD.
- With the exception of Becker 2004, AD is included as an AM in the reports.
- When available, OR and CI as reported in the Baumgartner 1998 and Osborn 2003 meta-analysis are depicted. In the Baumgartner publication, the OR and CI were reported only for AM for PHF-W vs CMF. The Osborn publication reports OR and CI for AM and AD for PHF-W vs CMF.

*Because the figures only depict OR and CI for studies up to 12 months of age, the D'Agata 1996 study is not shown as outcomes were measured only at 4 years of age.

Calculation of Odds Ratios and 95% Confidence Intervals

OR and 95% CI were calculated from the actual data presented in each study that did not report the data in this manner.

The following variables were used:

a = # of infants in the intervention group with AM or AD
b = # of infants in the intervention group without AM or AD
c = # of infants in the control group with AM or AD
d = # of infants in the control group without AM or AD

The equation used to calculate the odds ratio is:

OR = (a/b) / (c/d)

This can be simplified to:

OR = (ad) / (bc)

To calculate the corresponding 95% confidence interval:

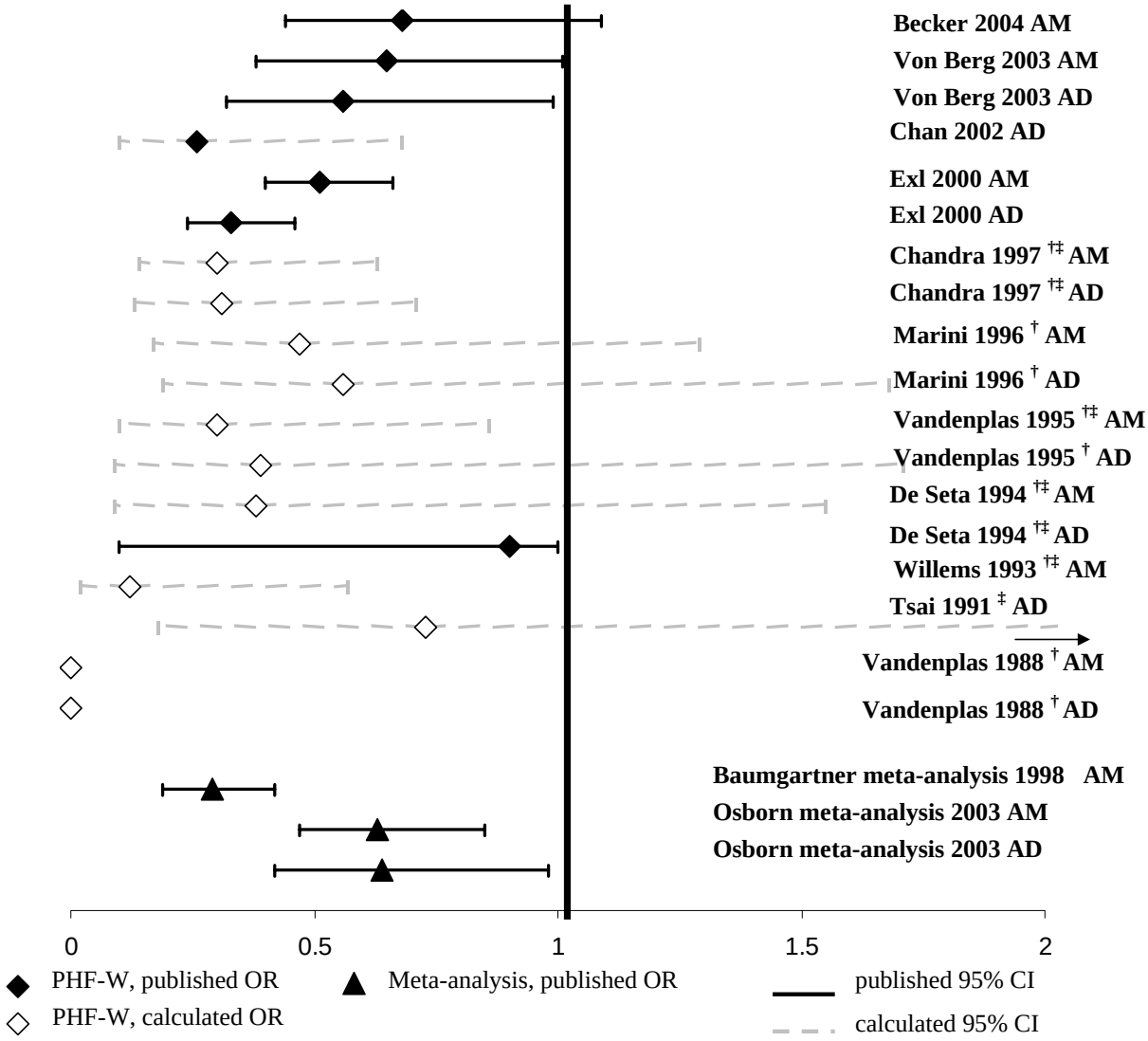
The equation used to calculate the 95% CI is:

$$95\%\ CI = (ad)/(bc)\ \exp\left(\pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}\right)$$

The equation can be simplified to:

$$\mathbf{95\%\ CI = (OR)\ exp}\left(\pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}\right)$$

Odds Ratio Summary of Nestlé PHF-W Intervention Studies of Allergic Manifestations (AM) and Atopic Dermatitis (AD) (Peer-Reviewed)



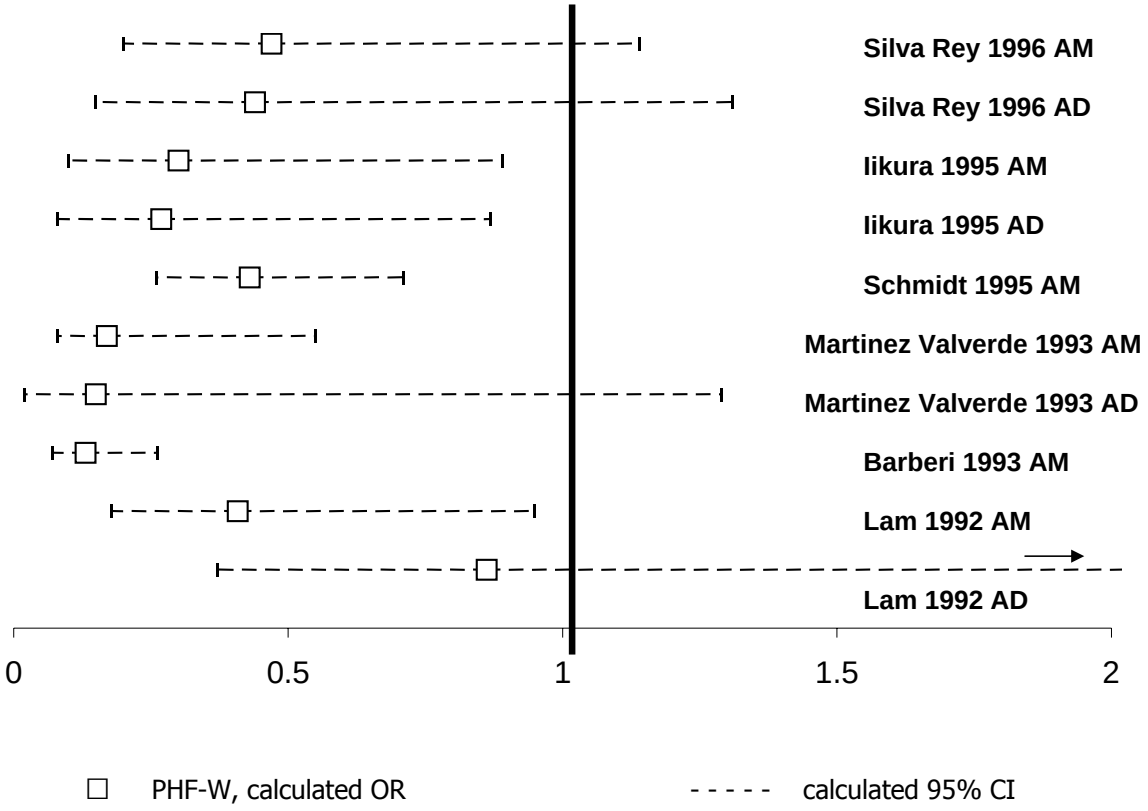
- *Graph depicts only published, peer-reviewed, prospective trials with data collection at timepoints ≤12 months. OR and CI shown in black are published values; OR in white and CI in dashed, gray lines are calculated values.*
- *For all studies except Becker 2004, AM includes AD as one of the allergic outcomes assessed; for Becker 2004, AM refers to asthma alone. For Exl (2000) AD refers to "skin symptoms." For Vandenplas (1988) AD refers to "dermatological symptoms."*
- *4 months: Vandenplas 1988; 6 months: Exl 2000, De Seta 1994; 12 months: Becker 2004, Von Berg 2003, Chan 2002, Chandra 1997, Marini 1996, Vandenplas 1995, Willems 1993, Tsai 1991. Data shown for Baumgartner reflect calculations for 12 months; Data shown for Osborn reflect calculations for the period defined as infancy.*
- *p-value for Marini 1996 AM is published as p<0.05; however, the calculated 95% CI indicates the upper limit of the* CI is >1.0
- *For De Seta 1994 AM, OR and CI depicted here are calculated, as the published value for the OR for AM at 6 months (0.3) is not consistent with the published CI (1.7-6.4). Published values for De Seta 1994 AD OR and CI are depicted here.*

† *Included in Baumgartner OR depicted here*

‡ *Included in Osborn OR depicted here*

In addition to the studies marked '†', this calculation includes the results of non-peer reviewed studies not depicted here

Odds Ratio Summary of Non-Peer-Reviewed Publications, Abstracts and Reports of Prospective Clinical Trials for Nestlé PHF-W vs CMF for Primary Prevention of Allergic Manifestations (AM) and Atopic Dermatitis (AD)



- *All OR and CI are calculated*
- *3 mo: Martinez Valverde (high-risk infants only); 6 mo: Lam, 12 mo: Silva Rey, Iikura, Schmidt, Barberi*
- *Iikura 1995 was a study of general population*

Appendix C-V: Summary tables of meta-analyses and select review papers

Meta-analytical reviews

Ref.	Studies included (Located in Appendix) [*]	Quotes from the Authors
Osborn 2003	Arshad 1992, Hide 1994, 1996* Chan-Yeung 2000 (II) Chandra 1989a, 1991, 1997 (II) Chandra 1989b* Chirico 1997 (II) De Seta 1994 (II) Halken 2000 (II) Juvonen 1994, 1996, 1999* Mallet 1992* Marini 1996 (II) Nentwich 2001+ Oldaeus 1997* Saarinen 1999, 2000a, 2000b, 2001* Szajewska 2001* Tsai 1991 (II) Vandenplas 1992, 1995 (II) Vandenplas 1993* Willems 1993 (II)	• "In high risk infants who are unable to be completely breast fed, there is evidence that prolonged feeding with a hydrolysed compared to a cow's milk formula reduces infant and childhood allergy and infant CMA [cow's milk allergy]. " • "Further trials are required to determine if significant clinical benefits persist beyond 5 years of age and if there is any additional benefit from use of an extensive compared to a partially hydrolysed formula." • "Benefits from the use of an extensively hydrolysed formula compared to an adapted cow's milk formula were found in high risk infants for the prevention of eczema in infancy (2 studies)….Benefits found from the use of a partially hydrolysed formula included reduced allergy incidence in infancy and childhood, asthma incidence in childhood, eczema incidence in infancy and prevalence in childhood, food allergy prevalence in childhood and CMA incidence in infancy. No significant difference was found in asthma incidence in infancy, rhinitis incidence in infancy or CMA prevalence in childhood." • "Further research is needed before a more costly extensively hydrolysed formula should be used in preference to a less costly partially hydrolysed formula." • "When babies are not exclusively breastfed, using hydrolysed infant formulas instead of ordinary cow's and soy milk formulas can reduce allergies in babies and children."
Ram 2003	Arshad 1992* Chandra 1989a (II) Mallet 1992* Marini 1996 (II) Tsai 1991 (II) Vandenplas 1992 (II) Zeiger 1989*	• "Breast-milk should remain the feed of choice for all babies. In infants with at least one first degree relative with atopy, hydrolysed formula for a minimum of four months combined with dietary restrictions and environment measures may reduce the risk of developing asthma or wheeze in the first year or life." • "Our review has shown that in infants at risk of atopic disease, supplementation of breast milk feeding with hydrolysed milk formula for four months or more in addition to dietary restrictions and house dust-mite reduction, was associated with a lower risk of wheeze in the first 12 months of life compared to standard cow's milk based formula. This protection appeared to persist to two years of age. However, these results should be interpreted with caution, because the number of studies was small and there were a range of other potentially active co-intervention."
Baumgartner 1998	Martinez Valverde 1993 (III) Chandra 1989a, 1991, 1992, 1997 (II) D'Agata 1996 (II) De Seta 1994 (II) Kraemer 1994+ Lam 1992 (unpublished report) Macagno 1989+ Marini 1990+ Marini 1996 (II) Mautone 1996+ Porch 1998+ Schmidt 1995 (III) Vandenplas 1988 (II) Vandenplas 1992, 1995 (II) Willems 1993 (II)	• "Breastfeeding or exclusive feeding of a moderately hydrolyzed formula (Nestlé HA formula) for at least three months in infants at high risk for the development of allergic disease, decreases the incidence of atopic manifestations until 60 months of age." • "Comparison of HA- [moderately hydrolyzed whey formula] with CMF [standard cow milk formula]-feeding employing meta-analysis indicates significantly lower odds ratios for the incidence of atopic symptoms in the HA groups for all age intervals between 3-6 and 60 months." • "The number needed to treat calculations estimate that between three and five high risk infants need to receive HA formula in order to protect one infant from atopic symptoms." • "At both 6 and 12 months, the meta-analyses suggest that the proportaion [sic] of infants who develop atopic symptoms in the standard cow milk formula group is about three to four times higher than the proportion in the HA group."

Baumgartner M, Brown CA, Exl BM, Secretin MC, van't Hof M, Haschke F. Controlled trials investigating the use of one partially hydrolyzed whey formula for dietary prevention of atopic manifestations until 60 months of age: an overview using meta-analytical techniques. Nutr Res 1998;18:1425-42.

Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

Ram FSF, Ducharme FM, Scarlett J. Cow's milk protein avoidance and development of childhood wheeze in children with a family history of atopy (Cochrane Review) In: *The Cochrane Library*, Issue 2, 2003. Oxford: Update Software.

* Study of an extensively hydrolyzed formula which did not include PHF-W and is therefore not included in summary tables or reference list.

+ Study which included PHF-W, but not CMF.

Select reviews discussing hydrolyzed (partially and extensively) infant formula and allergy prevention

Reference	Relevant studies cited (Located in Appendix)	Quotes from the Authors
Chandra 2002	Arshad 1992* Chandra 1989a, 1991 (II) Chandra 1989 b* Halken 2000+ Marini 1990+ Marini 1996 (II) Vandenplas 1992 (II) Willems 1993 (II) Zeiger 1989, 1995*	• "In all infants, especially in those with parental history of allergy, exclusive breast feeding for 4 months or longer, dietary precaution by the lactating mother, use of a hydrolyzed formula, and delayed introduction of egg, fish, and peanut have considerable value in preventing food allergy, eczema, asthma and other allergic manifestations." • "Both extensively hydrolyzed formula (eHF) and partially hydrolyzed formulas (pHF) reduce the incidence of allergy in infants, particularly among those with a family history of atopy." • "The high and rapidly increasing incidence of atopic disease in many industrialized countries and the difficulties in accurately selecting infants at risk of allergic disease has led many to suggest that allergy prevention measures should be applied to *all* infants, not only those considered to be at high risk of allergies."
Exl 2001	Arshad 1992, Hide 1994* Chandra 1989a, 1991, 1997 (II) Chandra 1989b* Exl 2000 (II) Halken 1992* Halken 1995* Halken 2000+ Hansen 1999+ Hide 1996* Marini 1996 (II) Oldaeus 1997* Oldaeus 1999* Porch 1998+ Schmidt 1995 (III) Vandenplas 1988 (II) Vandenplas 1992, 1995 (II) Willems 1993 (II) Zeiger 1989, 1995* Zeiger 1992*	• "The recommendations of nutritional committees for infants with a familial elevated risk of allergies are for exclusive breastfeeding over the first 4 to 6 months of life, delayed introduction of weaning foods, and –if necessary— supplementation of breastfeeding with a hydrolyzed infant formula proven for its preventive effect. However, there is still no final consensus on whether extensively or moderately hydrolyzed formulae are preferred if exclusive breastfeeding is not an option." • "Additionally, pHF [partially hydrolyzed formulas] are more palatable and less expensive than many eHF [extensively hydrolyzed formulas], and may therefore more readily replace regular cow's milk formulae in routine infant nutrition. Nonetheless, eHF may be favored during the first weeks of life for the 3% to 5% of infants with an extremely high risk of allergy according to bifamilial allergies and/or elevated cord blood-IgE." • "In conclusion, the results of recently published studies provide considerable evidence to suggest that pHF formulae are as effective as EHF in short- and long-term allergy prevention in high-risk non- or partially breastfed infants. The pHF formulae appear to induce a higher degree of oral tolerance….In addition, pHF are advantageous over most eHF in cost effectiveness and taste preference. In terms of allergy prevention, there are still no conclusive data from adequate and well-controlled studies to demonstrate whether eHF or pHF formulae have the greater protective effect. Regarding normal infant nutrition, pHF is proven to be a better alternative than cow's milk protein formulae."

* Study of an extensively hydrolyzed formula which did not include PHF-W and is therefore not included in summary tables or reference list.
+ Study which included PHF-W, but not CMF.

Select reviews discussing hydrolyzed (partially and extensively) infant formula and allergy prevention (continued)

Reference	Relevant studies cited (Located in Appendix)	Quotes from the Authors
Schoetzau 2001	Chandra 1989a, 1991, 1997 (II) Chandra 1989b* De Seta 1994 (II) Halken 1993* Mallet 1992* Marini 1996 (II) Oldaeus 1997* Porch 1998+ Vandenplas 1992, 1995 (II)	• "For more than 50 years, extensive hydrolysates have been successfully used for the treatment of infants with cow's milk protein allergy. There is no scientific controversy concerning the therapeutic efficacy of these formulas, thus clinical practice has given sufficient evidence of their reduced allergenicity. However, extensively hydrolysed formulas (eHF) are expensive to produce which limits their use for preventive purposes on a large scale. Furthermore, they have an unpleasant smell and taste which decreases their acceptance by infants and mothers. In the 1980s, pHFs [partially hydrolysed formulas] were developed to compensate these disadvantages. Since then, several studies on pHFs were performed, but they do not allow unequivocal inferences concerning and allergy preventive effect." • "The comparison of exclusively test- and control formula-fed groups showed a uniform tendency towards allergy protection in studies with partial hydrolysates." • "We conclude from this review that clinical research on the preventive effect of hydrolysed formulas in high risk infants is insufficient. Questions to be solved are whether eHFs are more efficacious than pHFs, and if yes, whether the difference in effect size is large enough to recommend these expensive formulas in allergy prevention on a large scale. The authors join the opinion of ESPACI and ESPGHAN [19], that more well-designed studies with an adequate power are needed which compare the allergy preventive effect of pHF and eHF with a standard infant formula."
Zeiger 2000	Arshad 1992, Hide 1996* Chandra 1997 (II) Halken 1993* Mallet 1992* Marini 1996 (II) Odelram 1996* Oldaeus 1997* Vandenplas 1995 (II) Zeiger 1989, 1992, 1995*	• "Both extensively and partially hydrolyzed PHs [protein hydrolysates] compared with cow's milk formula or soy formula have been reported to reduce atopic dermatitis, CMA [cow's milk allergy], and specific cow's milk IgE and even asthma. Outcomes appear similar to exclusive breast-feeding." • "The required sample sizes in a randomized 1:1 study needed to determine a 50% reduction in CMA with 95% certainty and 80% power with control group CMA prevalences estimated at the low end of 10% (5-fold higher prevalence than in unselected normal subjects) or high end of 20% (10-fold higher prevalence than in unselected normal subjects) would require cohort sizes of 948 or 474 high-risk newborns, respectively. No PH investigation has yet approached these sample sizes, and therefore it should not be unexpected that there are still no definitive data on the allergy-preventive effects of PH." • "As such, these studies require further confirmation with a definitive prospective, randomized masked, food challenge study that determines whether PHs prevent CMA before PHs are proclaimed effective and safe for the prevention of atopy in infants at high risk for atopy. Extensive PHs are more hypoallergenic and hypoimmunogenic but also are more costly and less palatable than partial PHs…" • "Until a definitive allergy-prevention study documents superiority of either the extensive hypoallergenic PH or the partial PH, it may be prudent to observe the advice of the European Society for Pediatric Allergy and Clinical Immunology regarding allergy prevention that extensively hydrolyzed hypoallergenic PH be the preferred choice for infant feeding, either as a substitute for or supplement to breast-feeding when breast-feeding is not elected or terminated early in high-risk infants." • "Should partial PHs be proved effective in reducing CMA, their use will certainly be cost effective at any level of CMA reduction, because their cost is comparable to that of cow's milk and soy formula. In contrast, if only the extensive PH formulas are effective in CMA prevention, several factors must also be considered in determining the net cost of CMA prevention using these formulas including prevalence of CMA in the high-risk cohort, extent of CMA reduction, their duration of use, and their cost differential ($2.75/day in the United States)."

* Study of an extensively hydrolyzed formula which did not include PHF-W and is therefore not included in summary tables or reference list.
+ Study which included PHF-W, but not CMF.

Select reviews discussing hydrolyzed (partially and extensively) infant formula and allergy prevention (continued)

Reference	Relevant studies cited (Located in Appendix)	Quotes from the Authors
Halken 1995	Arshad 1992, Hide 1994* Chandra 1989a, 1991 (II) Chandra 1989b* Halken 1993* Host 1995* Vandenplas 1988 (II) Vandenplas 1992 (II) Zeiger 1989, 1992*	• "Partially hydrolysed formulas (pHF) may be effective in allergy prevention, but due to draw backs of study design and lack of documentations pHF cannot be recommended at present. The results of studies comparing the preventive effect of eHF [extensively hydrolyzed formula] and pHF are awaited." • "In high-risk infants fed exclusively breastmilk and/or eHF combined with avoidance of cows milk proteins and solid foods during at least the first four months of life a reduction of the cumulative incidence of food allergy and atopic dermatitis during the first 2-4 years of life is found. The protective effect on the development of cow milk allergy is a real prevention and not only a postponement of the onset of symptoms. No studies have demonstrated a preventive effect of dietary measures as regards asthma/inhalant allergy, at present until the age of four years." • "At present EHF are recommended for avoidance of cow's milk. The results of studies comparing the preventive effect of EHF and PHF are awaited."

References:

Chandra RK. Breast feeding, hydrolysate formulas and delayed introduction of selected foods in the prevention of food hypersensitivity and allergic disease. Nutr Res 2002;21:125-35.

Exl BM. A review of recent developments in the use of moderately hydrolyzed whey formulae in infant nutrition. Nutr Res 2001;21:355-79.

Halken S, Jacobsen HP, Host A, Holmenlund D. The effect of hypo-allergenic formulas in infants at risk of allergic disease. Eur J Clin Nutr 1995;49:S77-83.

Schoetzau A, Gehring U, Wichmann HE. Prospective cohort studies using hydrolysed formulas for allergy prevention in atopy-prone newborns: a systematic review. Eur J Pediatr 2001;160:323-32.

Zeiger RS. Dietary aspects of food allergy prevention in infants and children. J Pediatr Gastroenterol Nutr 2000;39:S77-86.

* Study of an extensively hydrolyzed formula which did not include PHF-W and is therefore not included in summary tables or reference list.
+ Study which included PHF-W, but not CMF.

Appendix C-VI: Nestlé Scoring of Selected Studies

Nestlé has evaluated, by two different methods, the design of all the published, peer-reviewed studies that investigate the use of PHF-W protein infant formula versus intact cow's milk formula as a means of reducing the risk of allergy manifestation in infants. The "rating" methods described in FDA's July 10, 2003 Guidance entitled "Interim Evidence-based Ranking System for Scientific Data" were used in establishing the ratings incorporated into the summary table at Appendix C-II. In choosing the studies that would be summarized in narrative fashion, in establishing the order in which they would be presented – and in Nestlé's internal determination that the body of evidence was worthy of filing this petition – the Company focused on five commonly accepted criteria reflecting on the integrity or validity of the resulting data. Using the scoring system explained below, Nestlé evaluated each of the studies on all five criteria.

Scoring system utilized to evaluate PHF-W studies: Five criteria for study integrity and validity were considered: dropout rate; definition of outcome criteria and diagnosis of allergy; compliance monitoring; formula blinding and randomization; assessment of effect modifiers. Each of the studies was rated for all five criteria on a three-point scale, with larger values denoting higher quality. The possible scores ranged from 5 to 15 points. If compliance was stated without information on monitoring, it was assumed only one measure was employed.

Category	1 point	2 points	3 points
Dropout rate	>20% or no information	10% - 20%	< 10%
Outcome criteria/diagnosis of allergy	No classification of symptoms	Classification without blinded observer	Classification with blinded observer
Compliance monitoring	None reported	One measure	More than one measure
Formula blinding and randomization	Neither	Either blinded or randomized	Blinded and randomized
Effect modifiers	None reported	1 – 2 reported	> 3 reported

A listing of the scoring for the peer-reviewed publications is below.

Study	Score	Comments
Von Berg (2003)	14	Drop out (2) + outcome/dx (3) + compliance (3) + Blind/Rand (3) + Mod (3)
Vandenplas (1992a, 1992b, 1995)	14	Drop out (2) + outcome/dx (3) + compliance (3) + Blind/Rand (3) + Mod (3)
Marini (1996)	13	Drop out (2) + outcome/dx (3) + compliance (3) + Blind/Rand (2) + Mod (3)
Chandra (1989, 1991, 1992, 1997)	13	Drop out (3) + outcome/dx (3) + compliance (1) + Blind/Rand (3) + Mod (3)
Exl (1998, 2000)	12	Drop out (3) + outcome/dx (2) + compliance (3) + Blind/Rand (1) + Mod (3)
Becker (2004), Chan-Yeung (2000)	11	Drop out (2) + outcome/dx (3) + compliance (2) + Blind/Rand (2) + Mod (2)
Chan (2002)	11	Drop out (1) + outcome/dx (3) + compliance (2) + Blind/Rand (2) + Mod (3)
De Seta (1994)	10	Drop out (1) + outcome/dx (2) + compliance (2) + Blind/Rand (2) + Mod (3)
Willems (1993)	10	Drop out (3) + outcome/dx (2) + compliance (2) + Blind/Rand (2) + Mod (1)
Vandenplas (1988)	8	Drop out (2) + outcome/dx (2) + compliance (1) + Blind/Rand (2) + Mod (1)
Tsai (1991)	7	Drop out (1) + outcome/dx (2) + compliance (1) + Blind/Rand (2) + Mod (1)
D'Agata (1996)	6	Drop out (1) + outcome/dx (2) + compliance (1) + Blind/Rand (1) + Mod (1)

With the exception of the study conducted by Exl and colleagues, all studies with an FDA quality factor of '+' also received the highest scores using this Nestlé system. In addition, these publications were all randomized, controlled intervention trials of Design Type 1, showing consistency between this scoring system and that outlined by the FDA.

Page 1: [1] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [2] Change	**Unknown**

Field Code Changed

Page 1: [3] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [4] Change	**Unknown**

Field Code Changed

Page 1: [5] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [6] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [7] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [8] Change	**Unknown**

Field Code Changed

Page 1: [9] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [10] Change	**Unknown**

Field Code Changed

Page 1: [11] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [12] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [13] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [14] Change	**Unknown**

Field Code Changed

Page 1: [15] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [16] Change	**Unknown**

Field Code Changed

Page 1: [17] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [18] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [19] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [20] Change	**Unknown**

Field Code Changed

Page 1: [21] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [22] Change	**Unknown**	

Field Code Changed

Page 1: [23] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [24] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [25] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [26] Change	**Unknown**	

Field Code Changed

Page 1: [27] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [28] Change	**Unknown**	

Field Code Changed

Page 1: [29] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [30] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [31] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [32] Change	**Unknown**	

Field Code Changed

Page 1: [33] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [34] Change	**Unknown**	

Field Code Changed

Page 1: [35] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [36] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [37] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [38] Change	**Unknown**	

Field Code Changed

Page 1: [39] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [40] Change	**Unknown**	

Field Code Changed

Page 1: [41] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [42] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [43] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [44] Change	**Unknown**

Field Code Changed

Page 1: [45] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [46] Change	**Unknown**

Field Code Changed

Page 1: [47] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted

Page 1: [48] Formatted	**usfairchm**	**1/27/2005 1:30 PM**

Formatted